PHOSPHATE TETHER-MEDIATED SYNTHETIC STUDIES– APPLICATIONS IN NATURAL PRODUCTS SYNTHESIS

BY

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Abstract

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The focus of this dissertation is the utilization of phosphate tether mediated approaches to synthesize bioactive natural products and their analogs in an efficient and effective manner. The several salient features, which are inherent to phosphate triesters, include: (i) orthogonal stability under acid conditions, (ii) leaving group ability, (iii) multivalent activation of carbinol centers, (iv) protecting group attributes, and serving as a (v) temporary tether that can be removed under various conditions. Taken collectively various transformations, including chemoselective reductions as well as oxidations of the exocyclic olefin, a diastereoselective cuprate addition and successful cross-metathesis of type I and type II olefins with the exocyclic double bond, all mediated by phosphate tether, have provided the facile synthetic routes towards the synthesis of several natural products. Application of this protocol toward the total synthesis of fostriecin and 8-*epi*-fostriecin are reported. Fostriecin, an antitumor antibiotic isolated from *Streptomyces pulveraceus*, is the most selective and potent inhibitor of protein phosphatases 2A and 4, known to-date (IC_{50}s 3.2 *n*M and 3 *n*M, respectively). It has been shown to be active against L1210 and P388 leukemia cells *in vivo* and *in vitro* against leukemia, lung, breast, and ovarian cancer cells. Synthetic studies related to diastereoselective ring-closing metathesis reaction, regioselective oxidation, diastereoselective Grignard addition and cross metathesis, all mediated by a temporary phosphate tether, have established a scalable route toward the goal of total and analog synthesis of fostriecin and 8-*epi*-Fostriecin. In addition to the aforementioned transformations, the coupling of orthogonal transformations in a multi-step, one-pot, sequential RCM/CM/H_2 process has also allowed for facile synthesis of advanced intermediates en route to the total synthesis of natural products. Application of three step, one-pot, sequential RCM/CM/H_2 protocol in a library amenable, efficient and modular synthesis of strictifolione and

(6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one are also discussed. Both *anti*-fugal natural products were synthesized in seven linear steps starting from readily available 1,3-anti-diene-diol without incorporating additional protecting groups.

To my family

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Phosphate Tether-Mediated Synthetic Studies–

Applications in Natural Products Synthesis

Contents Page #

Contents (continued) Page #

Contents (continued) Page #

Abbreviations

Ac	acetyl
AcOH	acetic acid
AChE	acetylcholinesterase
ACE	angiotensin-converting-enzyme
ADME	absorption, distribution, metabolism and excretion
Aq	aqueous
BA	brønsted acid
BBN	borabicyclononane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
Boc	*tert*-butyloxycarbonyl
BRSM	based on starting material
c	concentration
cat.	catalytic
Cbz	carbobenzyloxy
CM	cross metathesis
CSA	camphorsulfonic acid
CuTC	copper thiophene 2-carboxylate
Cy	cyclohexyl
d	day
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DIAD	diisopropyl azodicarboxylate

DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMP	desmartinperiodinane
DTE	S-[(2-hydroxyethyl)-sulfidyl]-2-thioethyl
EWG	electron Withdrawing Group
FDT	freeze degas thaw
Fm	Flurenylmethyl
h	hours
HDA	hetero Diels-Alder
HG–II	Hoveyda-Grubbs Catalyst 2nd Generation
HF	Hydrogen fluoride
HMPA	Hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HWE	Horner Wardsworth Emmons
HSL	Hormone sensitive lipase
IC_{50}	inhibitory concentration at 50%
i-Pr	isopropyl
IR	infrared radiation
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LLS	Longest linear sequence
LG	leaving group
M	molarity
m-CPBA	*meta*-chloroperoxybenzoic acid
Mes	mesitylene
MOM	methoxymethyl ether
MS	molecular sieves
n-BuLi	*n*-butyllithium
NHC	N-heterocyclic carbene

NMO	*N*-methyl-*N*-morpholine-*N*-oxide
NMM	N-methylmorpholine
NMR	nuclear magnetic resonance
NMP	N-methylpyrrolidinone
NTBSCl	N-*tert*-Butylbenzenesulfinimidoyl Chloride
Nuc	nucleophile
o-NBSH	*ortho*-nitrobenzenesulfonyl hydrazide
Phth	phthaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PP1	Protein phosphatase -1
PP2A	Protein phosphatase-2A
PP4	Protein phosphatase -4
PPTS	pyridinium *para*-toluene sulfonate
psi	pounds per square inch
PTSA	*p*-toluenesulfonic Acid
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
RCM	ring closing metathesis
RT	room temperature
SAR	structure activity relationship
SATE	S-acylthioethyl
Ser	serine
SM	starting material
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
t-Bu	*tert*-butyl
TCQ	tetrachloroquinone

TEA	triethylamine
TESH	triethylsilane
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	triphenylphosphine
Ts	*para*-toluene sulfonyl
TS	total number of steps

Chapter 1

Phosphates in Biology and Chemical Synthesis

1.1 Introduction:

Phosphates are ubiquitous in nature and play a multi-faceted role in living systems where enzyme-catalyzed processes predominate. They also serve as a pivotal functional groups in several biologically active phosphate-containing natural products. In addition, the unique properties inherent to phosphates and their mono, di- and triester forms also enable their utility in synthesis. This chapter will give an account of the importance of the phosphate-containing natural products and methods for phosphate installation in them. A short account will follow on phosphate prodrug strategies for medicinally important non-phosphate-containing, as well as phosphate-containing, molecules. The chapter will end with a section on recent advances in the use of phosphates in synthesis, including previous studies completed in our group.

1.2 Phosphate containing natural products

There are several reports on phosphate-containing molecules that are known to possess various biological activities. This chapter will highlight the biological significance of the calyculins, fostriecin, phoslactomycins, leustroducsins, cytostatin, enigmazole A, cyclophostin, moenomycin A, and FR901483, as well as detail synthetic studies for phosphate installation.

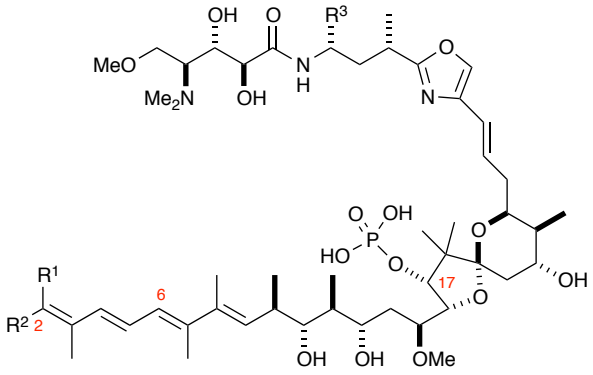
1.2.1 Calyculins

The calyculins are highly toxic metabolites isolated from the marine sponge *Discodermia calyx* by Fusetani and co-workers.[1] Calyculin A, the first member in the family, was isolated in 1986 from a sponge collected in the gulf of Sagami, near

Tokyo Bay (Figure 1).[1] Calyculin A and its analogs have been found to be potent inhibitors of protein phosphatase-1 (PP1) and protein phosphatase-2A (PP2A), which are key enzymes involved in signaling pathways associated with human disease.[2] Most importantly, studies involving structure activity relationships (SAR) of the calyculins indicate that the phosphate, the C13-hydroxyl, and the hydrophobic polyketide tail are essential for their inhibitory activity.[3] The fascinating structural features associated with calyculins, which contain 15 chiral centers, a cyano-capped tetraene unit, a phosphate-bearing spiroketal, an α-chiral oxazole, and a trihydroxylated γ-amino acid, have identified the calyculin family as a synthetically challenging set of natural products, and as such, only six total and formal syntheses of molecules within this family have been reported to date (see Evans, Masamune, Shioiri, Smith, Armstrong and Barrett).[4]

In 2010, Koskinen and co-workers broadly reviewed the synthetic efforts toward this interesting natural product.[5] The purpose of this section will be to highlight methods aimed at the installation of the phosphate group and provide a brief summary of each approach (Figure 1)

Figure 1: *Calyculin family of molecules and a summary of the reported syntheses.*

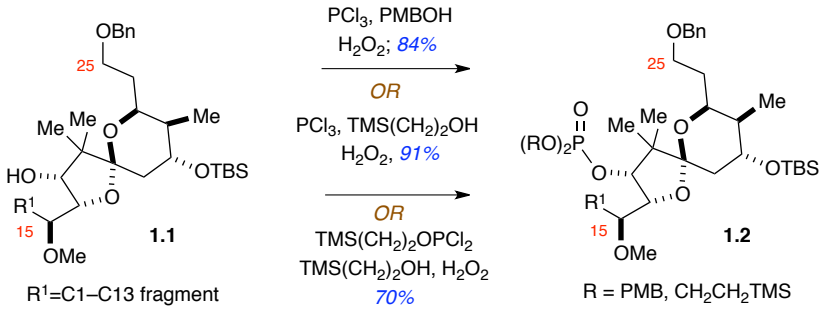


Calyculins: R^1: R^2: R^3: C6-C7 geometry				
A	CN	H	H	E
B	H	CN	H	E
C	CN	H	CH3	E
D	H	CN	CH3	E
E	CN	H	H	Z
F	H	CN	H	Z
G	CN	H	CH3	Z
H	H	CN	CH3	Z

Group	Target	Year	Longest linear sequence(LLS)
Evans	*ent*-Calyculin A	1992	36
Masamune	Calyculin A	1994	45
Shioiri	Calyculin A	1996	32
Smith	*ent*-Calyculin A	1998	37
Armstrong	Calyculin C	1998	30
Barrett	*ent*-Calyculin A	2001	34

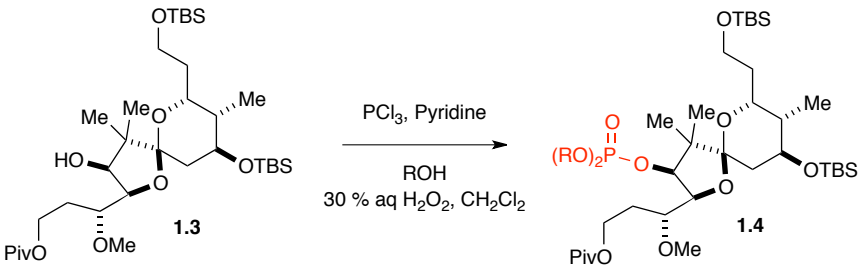
Among all the fascinating structural features within the calyculin family, the presence of a phosphate group at C17 is of high importance, due to promising biological activity, as well as structural challenges for its installation. In addition, because of the steric environment at C17 and shielding within the spiroketal core, it could be assumed that a reactive electrophile would be required to introduce the phosphate group at C17 (Scheme 1).

Scheme 1



In 1992, Evans and coworkers accomplished the first total synthesis of *ent*-calyculin A (Figure 1).[4] In their synthesis, phosphorylation at C17 was accomplished via coupling of C1–C25 fragment **1.1** with PCl_3, followed by treatment with *p*MeO-benzyl alcohol (PMBOH) and *in situ* oxidation with H_2O_2, to yield phosphate triester **1.2**. The resulting phosphate containing C1–C25 fragment was then subjected to four more reactions to complete the total synthesis of *ent*-calyculin A. In addition, model studies performed by Evans and coworkers to install the C17 phosphate group illustrated that both $(BnO)_2P(O)Cl$ and $POCl_3$ were not electrophilic enough to react with the sterically-hindered C17 alcohol, while more electrophilic PCl_3 was successful in phosphorylation (Scheme 1).[6] Further studies revealed that all four evaluated protecting groups were stable under HF•pyridine conditions, while only the *p*-$MeOC_6H_4CH_2$ diester protection was fully cleaved with CH_3CN, 48% aq. HF and H_2O (Scheme 2). Most notably, the 2-(trimethylsilyl) ethyl-protecting group proved to be the most robust upon exposure to all conditions.

Scheme 2



Stability of phosphates protecting groups.

R	HF•Pyr	HF, CH_3CN	KHMDS
$NCCH_2CH_2$	Yes	Yes	No
$Me_3SiCH_2CH_2$	Yes	Yes	Yes
$C_6H_5CH_2$	Yes	Yes	
p-$MeOC_6H_4CH_2$	Yes	No	

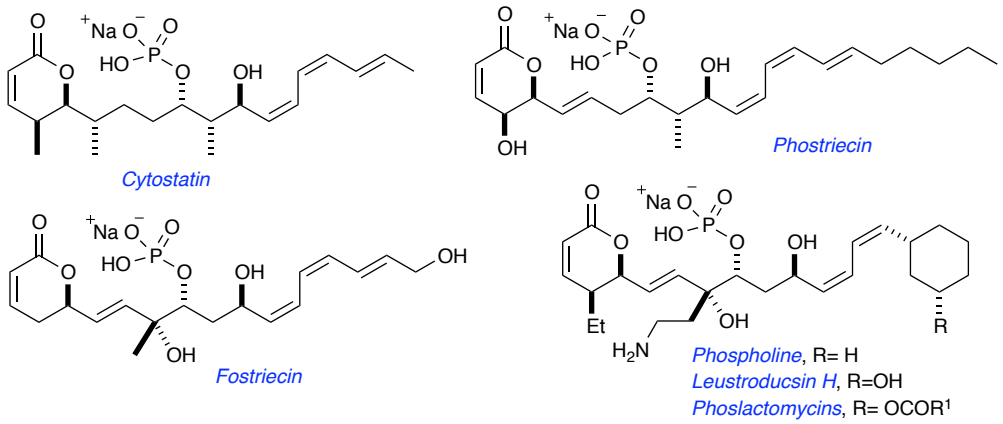
In addition to the studies described above, the Masamune group also reported model studies on the stability of phosphate protecting groups—namely, allyl and 2-(trimethylsilyl) ethyl-protected phosphates—within the context of a similar fragment to **1.3** and found that the deprotection of diallyl phosphate triesters, upon treatment with $Pd(PPh_3)_4$, did not provide the corresponding monoester, even under a variety of conditions (time and temperature).[7] More importantly, they also found that the 2-(trimethylsilyl) ethyl-protected triester was tolerant of a number of subsequent reaction conditions, including amide bases (KHMDS) and typical Stille coupling conditions, and can be completely removed via treatment with CH_3CN/47% HF/H_2O = 8.5/0.5/1). Of notable importance, Masamune and coworkers were able to carry out 12 consecutive steps, including hydrogenation, oxidation, Julia-Lythgoe olefination, and Stille coupling, while maintaining the integrity of a TMS-protected phosphate.[8]

With this information in hand, several groups applied the same protocol developed by the Evans and Masamune groups in their seminal syntheses of calyculin A.

1.2.2 Fostriecin, Phoslactomycins, Leustroducsins

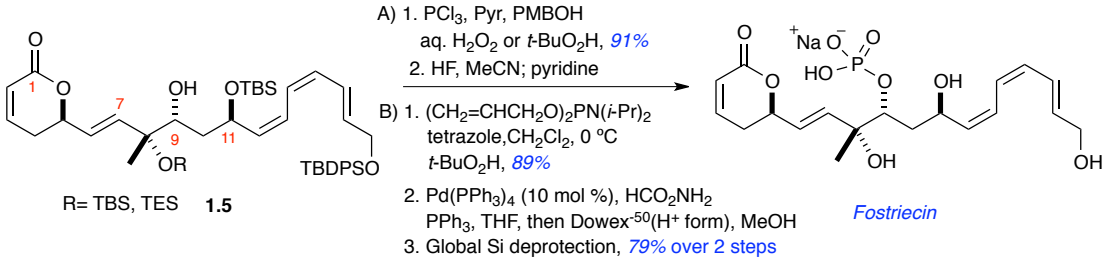
Fostriecin, a phosphate monoester isolated in 1983 from *Steptomyces pulveraceus*, has shown impressive *in vivo* antitumor activity, as well as *in vitro* cytotoxicity against a broad range of cancer cell lines, including leukemia, lung cancer, breast cancer and ovarian cancer (Figure 2).[9] Most notably, this significant biological activity has been tied to its remarkable ability to selectively inhibit protein phosphatase-2A (PP2A) and protein phosphatase-4 (PP4), which results in these various cytotoxic properties. In combination with these biological activities, the unique structure of fostriecin that consists of an α,β-unsaturated lactone, C9-phosphate, C8 stereo center, and (*Z, Z, E*)-triene have attracted a substantial amount of attention from the synthetic community, and a number of synthetic and biological studies of fostriecin and its analogs have been reported, including 8 total syntheses and 3 formal syntheses.[10] Furthermore, SAR studies performed by Boger and coworkers revealed that the α,β-unsaturated lactone, the completely deprotected phosphate at C9, and the C11 hydroxyl group are essential for the potent biological activity seen in fostriecin.[11] A detailed account on synthetic approaches and the corresponding SAR studies will be discussed in chapter 2.

Figure 2 *Fostriecin family of phosphate-containing natural products.*



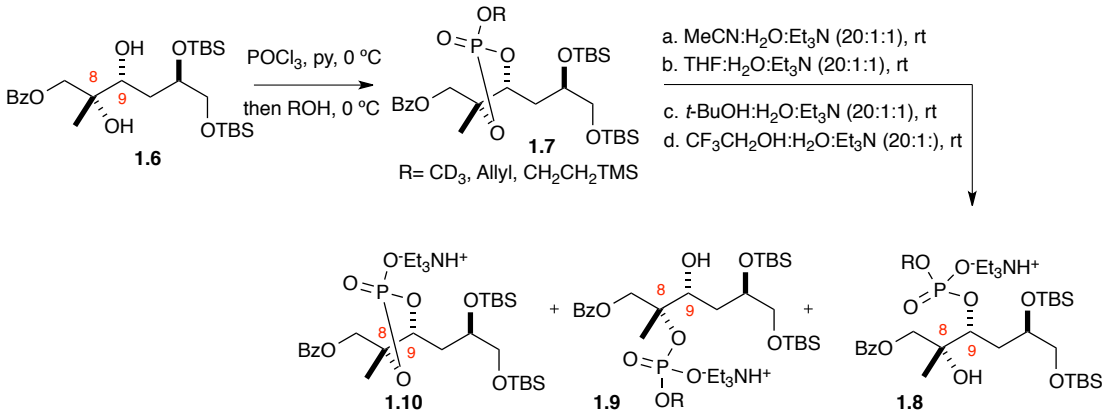
In general, the reported total, as well as formal, syntheses of fostreicin have all involved the late-stage installation of the C17 phosphate group, and both phosphoramidite- and phosphite-mediated methods have been employed for phosphorylation, to yield both allyl- and PMB-protected phosphates, respectively (Scheme 3).[10] In 2001, Boger and coworkers observed extensive degradation and olefin isomerization of the phosphorylated version of **1.5** during phosphate PMB-deprotection with prolonged exposure to unbuffered HF, and further attempts at PMB-removal with HF-pyr did not afford cleanly deprotected product. Thus, in their synthesis, Boger and coworkers employed a two-stage deprotection, where treatment with HF (15 min) resulted in PMB-deprotection and subsequent addition of pyridine allowed for silyl removal of C8-, C9-, and C18-protected alcohols.[10a] Conversely, when allyl-protected phosphates were utilized, Pd-catalyzed reductive deallylation and HF-pyridine were employed to unveil deprotected-fostreicin in good overall yield.[10e]

Scheme 3



In 2003, Imanishi and coworkers highlighted a selective cleavage of cyclic phosphate en route to fostriecin.[10] Though monophosphorylation with $POCl_3$ of the C9 hydroxyl was unsuccessful within the course of their synthesis, Imanishi and coworkers demonstrated that dipodal coupling of $POCl_3$ with the C8 tertiary hydroxyl and the C9 hydroxyl in diol substrate **1.6** provided cyclic phosphate **1.7** as an alternative pathway to install the phosphate group in fostreicin (Scheme 4).[10f] Model studies with diol substrate **1.6** revealed that hydrolytic cleavage of cyclic phosphoester **1.7** in 2,2,2-trifluoroethanol (Method D) provided promising results with respect to both chemical yield and regioselectivity to afford phosphate **1.8**. The authors postulated that, upon hydrolysis, the endo-cyclic P–O bond of **1.7** is cleaved more easily than the exo-cyclic P–O bond due to a stereoelectronic effect resulting from the 5-membered ring conformation in the trigonal bipyramidal transition state.[12] Therefore, cleavage of the more sterically hindered P-O bond occurred preferentially to provide the required monoester **1.8** over the exo-cyclic P–O bond opened product **1.9**. Notably, the authors also mentioned that phosphorylation via cyclic phosphate intermediate **1.7** was far more effective (23%) in comparison to direct phosphorylation (7%).[10f]

Scheme 4



R	*Method*	(**1.8:1.9:1.10**)	*R*	*Method*	(**1.8:1.9:1.10**)
CD_3	a	54:15:31	CD_3	d	70:17:13
	b	57:14:29	allyl	d	77:14:9
	c	66:15:13	CH_2CH_2TMS	d	72:14:14

1.2.3. *Phoslactomycins, Leustroducsins*

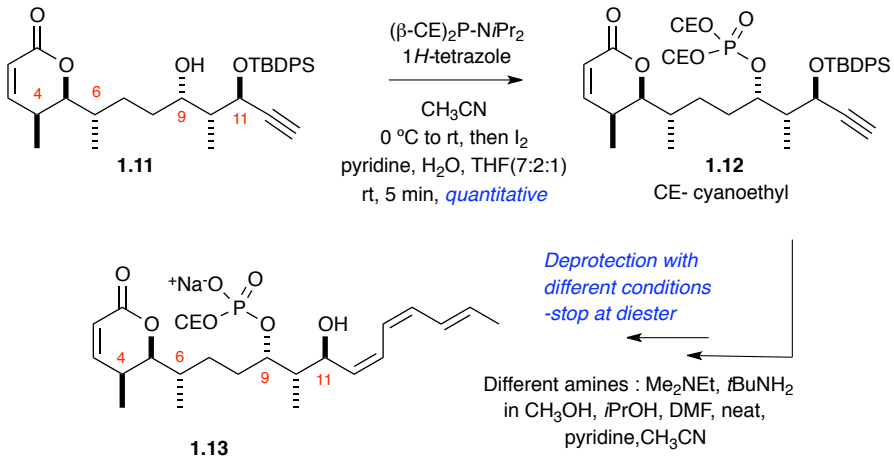
Phoslactomysins (A-F), phospholine and leustroducsins (A-C) (Figure 2) are phosphate-containing, natural products isolated from *Streptomyces nigrescens*, *Streptomyces hygroscopicus* and *Streptomyces platensis*, respectively. These are known to possess potent antitumor, antibacterial, and antifungal activities, as well as inhibitory activity for human protein phosphatase 2A (PP2A), that have been directly linked to the interaction of the phosphate group within enzyme binding sites.[13] Key structural features of these families bear striking resemblances to fostriecin but differ slightly at C4 (ethyl group), C8 (2-aminoethyl side-chain, instead of simple methyl group) and C15 (cyclohexyl substituted (*Z, Z*)-diene, instead of a labile (*Z, Z, E*)-triene subunit). In addition, the phospholactomycins and leustroducsins share nearly identical core structures, differing only at the substitution at C18. Several synthetic

studies[14] towards the construction of these families of molecules, as well as their analogs, have been reported, including two total syntheses for both phoslactomycin B (Kobayashi, 2006 and Hatakeyama, 2008) and leustroducsin B (Fukuyama, 2003 and Imanishi, 2008), as well as one total synthesis for phoslactomycin A (Koert, 2009).[15] In all these syntheses, the C9 phosphate was introduced via one of two previously described pathways: (1) allyl-protected phosphoramidite chemistry; or (2) hydrolytic cleavage of a cyclic phosphate, which are discussed in detail in the portion of this section devoted to the synthesis of fostriecin (Schemes 3 and 4).

1.2.4. Cytostatin

Cytostatin (Figure 2), another potent and selective PP2A and PP4 inhibitor, belongs to the fostriecin family of natural products and possesses similar characteristic structural units, including a phosphate monoester, (*Z*, *Z*, *E*)-triene, and α, *β*-unsaturated lactone.[16] In addition to the biological activity common to this family, cytostatin has been shown to inhibit the adhesion of B16 melanoma cells to

Scheme 5



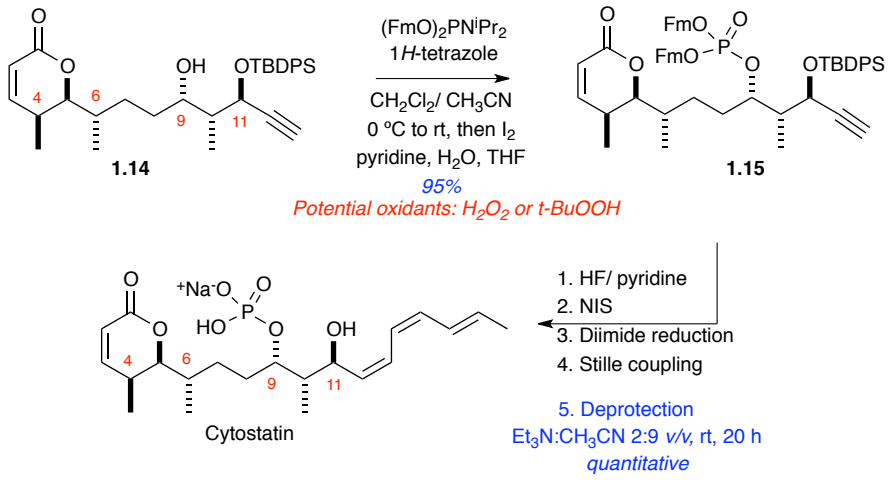
laminin and collagen, display antimetastatic and cytotoxic activity, and induce apoptosis of B16 melanoma cells at sub-μM concentrations.[16] To date, several (3) total and analog syntheses, as well as synthetic studies were reported.[17]

In 2002, Waldmann reported the first total synthesis of cytostatin, involving the late-stage introduction of phosphate group prior to the incorporation of the C12–C18 triene (via Stille coupling).[17a,b] Phosphate installation to **1.11** via phosphoramidite coupling, in the presence of 1*H*-tetrazole, followed by the oxidation with oxidation with I_2 in THF:pyridine:H_2O 7:2:1, provided phosphorylated product **1.12** (Scheme 5). Due to obvious incompatibilities with planned successive steps, acid- and Pd^0-labile phosphate protecting groups, as well as groups sensitive to hydrogenation conditions (benzyl group), were avoided, and synthetic studies instead utilized base-labile phosphate protecting groups, such as 2-cyanoethyl group and 9-fluorenylmethyl (Fm) group.[18] However, efforts to fully deprotect the cyanoethyl group with amine bases (Me_2NEt, tBuNH$_2$ or Et_3N, DBU with TMSCl) in the presence of various solvents (CH_3OH, 2-propanol, DMF, neat, pyridine, acetonitrile) were fruitless; thus, this route was limited to the formation of phosphate diester **1.13**, instead of the desired monoester (Scheme 5).

In contrast, the successful installation of the 9-fluorenylmethyl-protected phosphate diester, via the coupling of **1.14** with phosphoramidite $(FmO)_2PN^iPr_2$, followed by oxidation with I_2 in THF:pyridine:H_2O 7:2:1, allowed access to **1.15** that was smoothly deprotected with excess Et_3N in CH_3CN, to afford the desired

phosphate monoester in cytostatin (Scheme 6).[17a,b] Later syntheses of cytostatin reported by Boger (2006)[17c] and Cossy (2007)[17e] also applied this phosphorylation-deprotection protocol.

Scheme 6

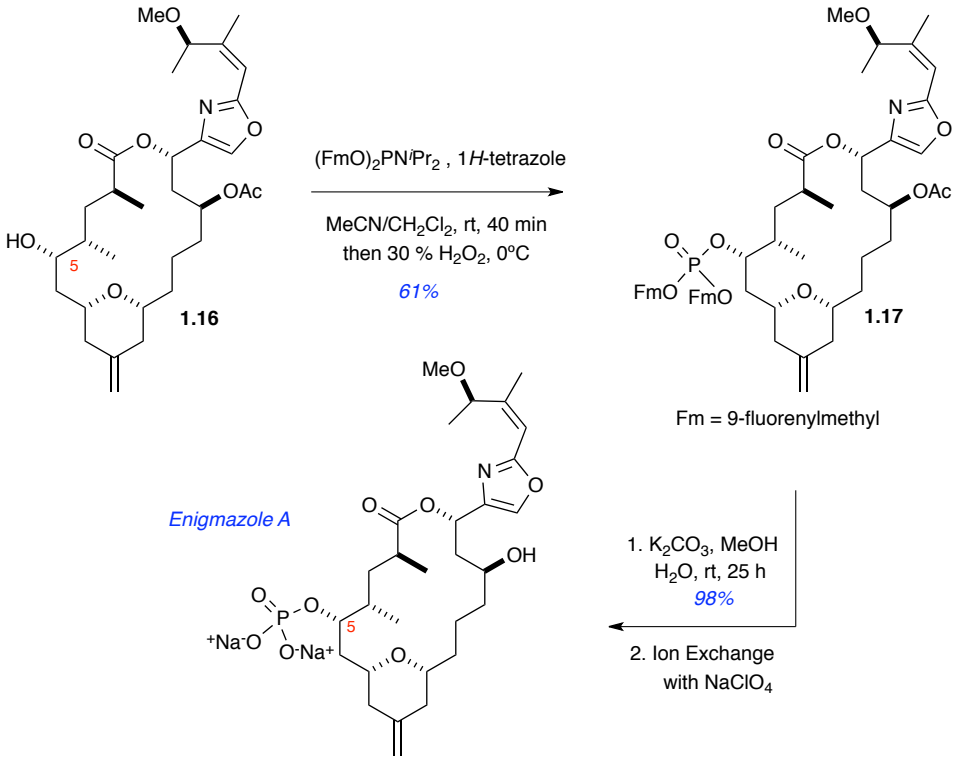


1.2.5. Enigmazole A

Enigmazole A, an 18-membered macrolide which contains a dianionic phosphate monoester, exo-methylene substituted tetrahydropyran ring and densely functionalized 2,4-disubstituted oxazole fragments, was one of the first phosphomacrolides isolated from a marine source (sponge, *Cinachyrella enigmatica*) and has been shown to exhibit significant *in vitro* cytotoxicity toward IC-2 mast cells.[19] Even though enigmazole A also shared several functional groups and structural features with calyculin A, it was shown to be inactive for both phosphatases (17 different types) and kinases (70 different types) at high-test concentration of 40 μg/ml. In 2010, Molinski reported the first total synthesis of enigmazole A in 22

steps.[20] Phosphorylation at the C5 hydroxyl group of **1.16** was successfully completed, utilizing the same protocol developed by Waldmann in cytostatin, via coupling with protected phosphoramidite $(OFm)_2PN{i}Pr_2$ and subsequent oxidation with H_2O_2 to afford phosphate triester **1.17** in 61% yield. Successive phosphate and acetate deprotection was achieved with K_2CO_3 in $MeOH/H_2O$ to generate enigmazole A as the disodium salt in excellent yield.

Scheme 7

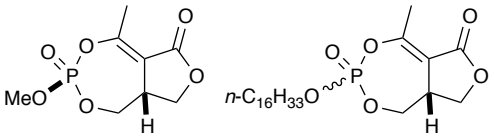


1.2.6. Cyclophostin and Cyclipostin P

Cyclophostin and cyclipostin P (Figure 3) are naturally occurring bicyclic organophosphates, which share the same structural core unit and differ only in phosphate triester subunits.[21] Cyclophostin (**8a**) is a potent acetylcholinesterase

(AChE) inhibitor isolated from a fermentation solution of *Streptomyces lavendulae* (strain NK901093), while closely related cyclipostin P (**8b**) is a potent inhibitor of hormone sensitive lipase (HSL).[21] In combination with this impressive biological activity, the interesting structural features of these seven-membered bicyclic enol-phosphate triesters, which possess a 7,5-fused butyrolactone ring and chirality at C3, as well as at phosphorus, have identified them as interesting synthetic and biological targets.

Figure 3: *Cyclophostin and cyclipostin P.*

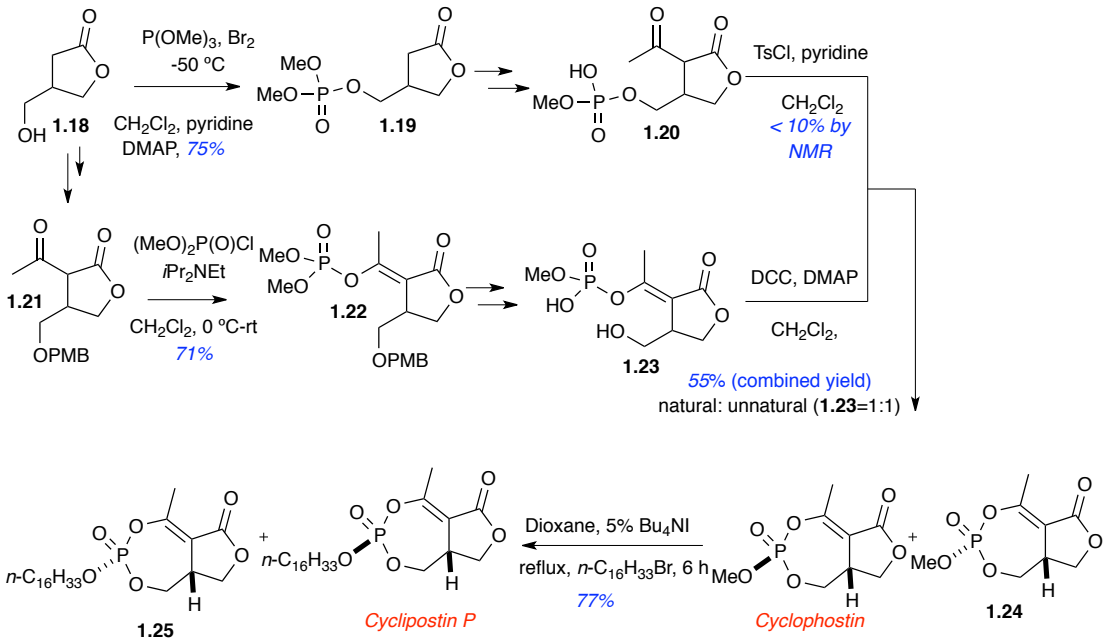


In 2011, Spilling and coworkers reported the first total syntheses of cyclophostin, its unnatural diastereomer and cyclipostin P, utilizing two different phosphorylation approaches.[22] The authors envisioned that cyclophostin could be accessed either through the phosphorylation of primary alcohol of **1.18** and subsequent installation and condensation with a distal acetyl group (in **1.20**) or through the selective phosphorylation of butyrolactone to selectively provide *E*-enol phosphate **1.21**, followed by PMB-deprotection and condensation with the distal primary alcohol (Scheme 8).

In light of this, primary alcohol **1.18** was phosphorylated with dimethyl bromophosphate, prepared *in situ* by reaction with $(MeO)_3P$ and Br_2, to afford phosphate triester **1.19** in 75% yield. This phosphorylated butyrolactone was

converted to acetyl lactone **1.20** via a two-step acylation-deprotection protocol involving alkylation with LiHMDS and acetyl chloride and demethylation with NaI, followed by protonation with Amberlite® (sulfonic acid) resin. However, cyclization of **1.20** via intramolecular condensation furnished the desired product in extremely low yield. Thus, utilizing the second proposed route, cyclization of enol phosphate **1.23**, prepared in several steps from **1.18** and dimethyl phosphorochloridate, provided the cyclic enolphosphates (natural and unnatural cyclophostin **1.24**) as 1:1 mixture of diastereomers that were separable via silica gel chromatography.

Scheme 8



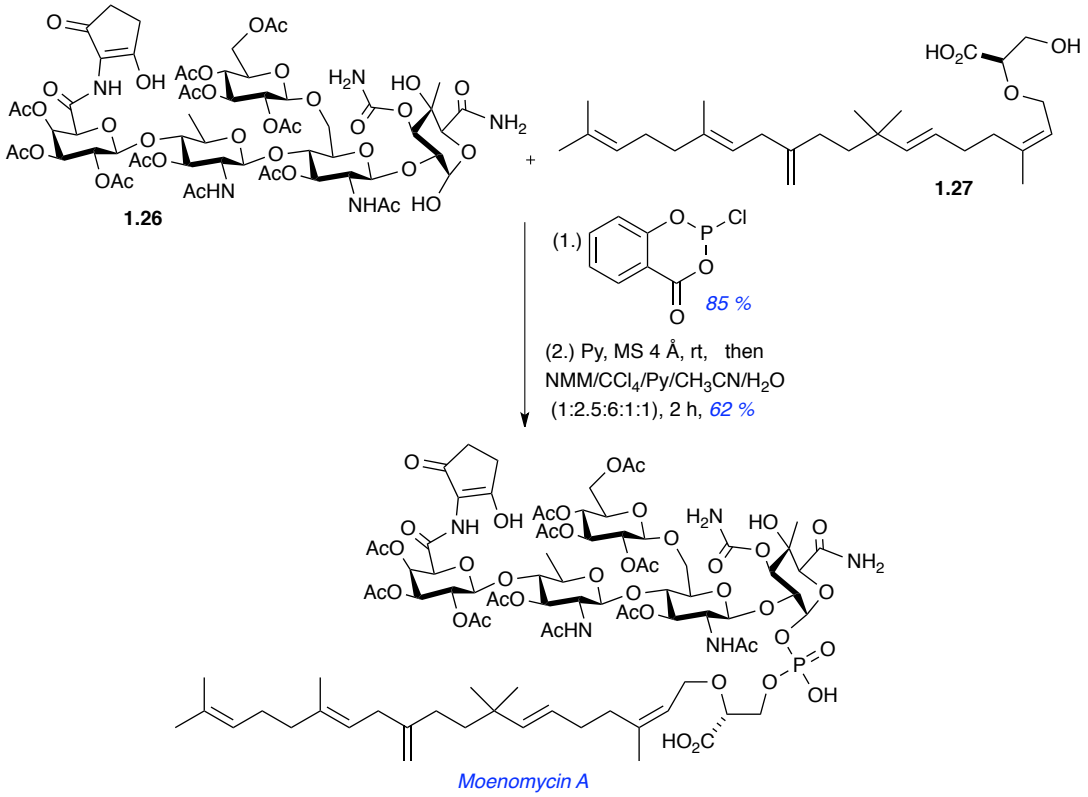
Finally, the family of cyclipostins and unnatural cyclipostins (**1.25**) were completed via demethylation of cyclophostin and **1.24** with Bu_4NI and subsequent

alkylation with the corresponding alkyl bromides to provide the desired phosphate triesters in good overall yield.

1.2.7. Moenomycin A

Moenomycin A, a potent antibiotic that inhibits bacteria cell wall synthesis, consists of a highly functionalized pentasaccharide attached to a polyprenyl chain via a unique phosphoglycerate linkage.[23,24] Since the isolation of moenomicin A in 1985, several synthetic studies have been reported.[25] In 2006, Kahne and coworkers reported the first and only total synthesis of moenomycin A.[26] In this synthesis, the authors utilized *H*-phosphonate chemistry to introduce the phosphate

Scheme 9

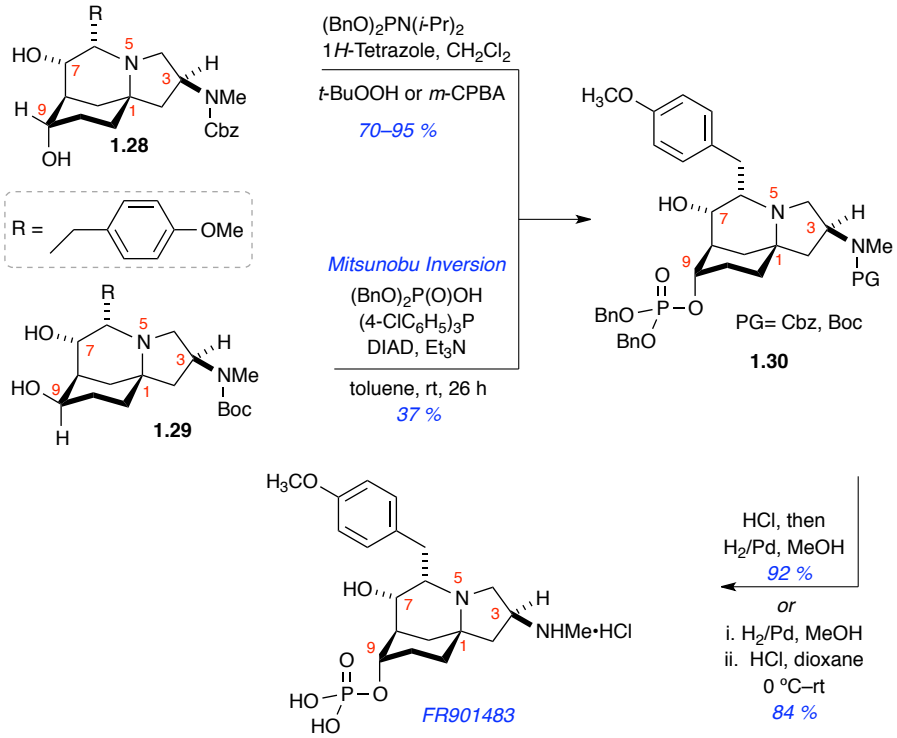


linkage, where pentasaccharide **1.26** and moenocinyl glycerate (**1.27**) were coupled with cyclic *H*-phosphoryl chloride (2-chloro-1,3,2-benzodioxaphosphorin-4-one), followed by regioselective oxidation with NMM in the presence of CCl_4, to yield moenomycin A in good yield (Scheme 9).

1.2.8. FR901483

FR901483 is a potent immunosuppressant that was isolated from the fermentation broth of the fungal strain *Cladobotryum sp.* NO. 11231 by the Fujisawa group in 1996.[27] In addition to this biological significance, the novel aza-tricyclic structure of FR901483 was a synthetically attractive feature, which has fueled efforts toward the completion of several elegant total syntheses,[28] as well as synthetic studies. In the reported syntheses, the methods utilized to install the C9 phosphate group were dependent upon the stereochemistry of the C9 alcohol in starting aza-tricyclic substrates **1.28** and **1.29** (Scheme 10). In the case where the C9-hydroxyl is axial (**1.28**), direct phosphorylation with dibenzyl-*N,N'*-diisopropyl phosphoramidite, in the presence of 1*H*-tetrazole, followed by oxidation with a peroxy acid,[29] was utilized to afford **1.30** in 70–95% yield. However, when the C9-hydroxyl is equatorial (**1.29**), Mitsunobu inversion with dibenzyl phosphoric acid (already discussed in the Mitsunobu section) was utilized to generate phosphorylated product **1.30** with suitable C9-stereochemistry. Notably, successful phosphorylation was achieved selectively at C9 in both approaches in the presence of the sterically crowded C7 hydroxy group. Finally, amine deprotection/phosphate debenzylation allowed access to the natural product FR901483 as the hydrochloride salt.

Scheme 10


R
HO
7
N
5
3
H
NMe
Cbz
H
9
1
OH
1.28
R =
OMe
R
HO
7
N
5
3
H
NMe
Boc
HO
9
1
H
1.29
(BnO)2PN(i-Pr)2
1H-Tetrazole, CH2Cl2
t-BuOOH or m-CPBA
70–95 %
Mitsunobu Inversion
(BnO)2P(O)OH
(4-ClC6H5)3P
DIAD, Et3N
toluene, rt, 26 h
37 %
H3CO
HO
7
N
5
3
H
NMe
PG
9
1
O
BnO
P
O
BnO
PG= Cbz, Boc
1.30
H3CO
HO
7
N
5
3
H
NHMe•HCl
9
1
O
HO
P
O
HO
FR901483
HCl, then
H2/Pd, MeOH
92 %
or
i. H2/Pd, MeOH
ii. HCl, dioxane
0 °C–rt
84 %

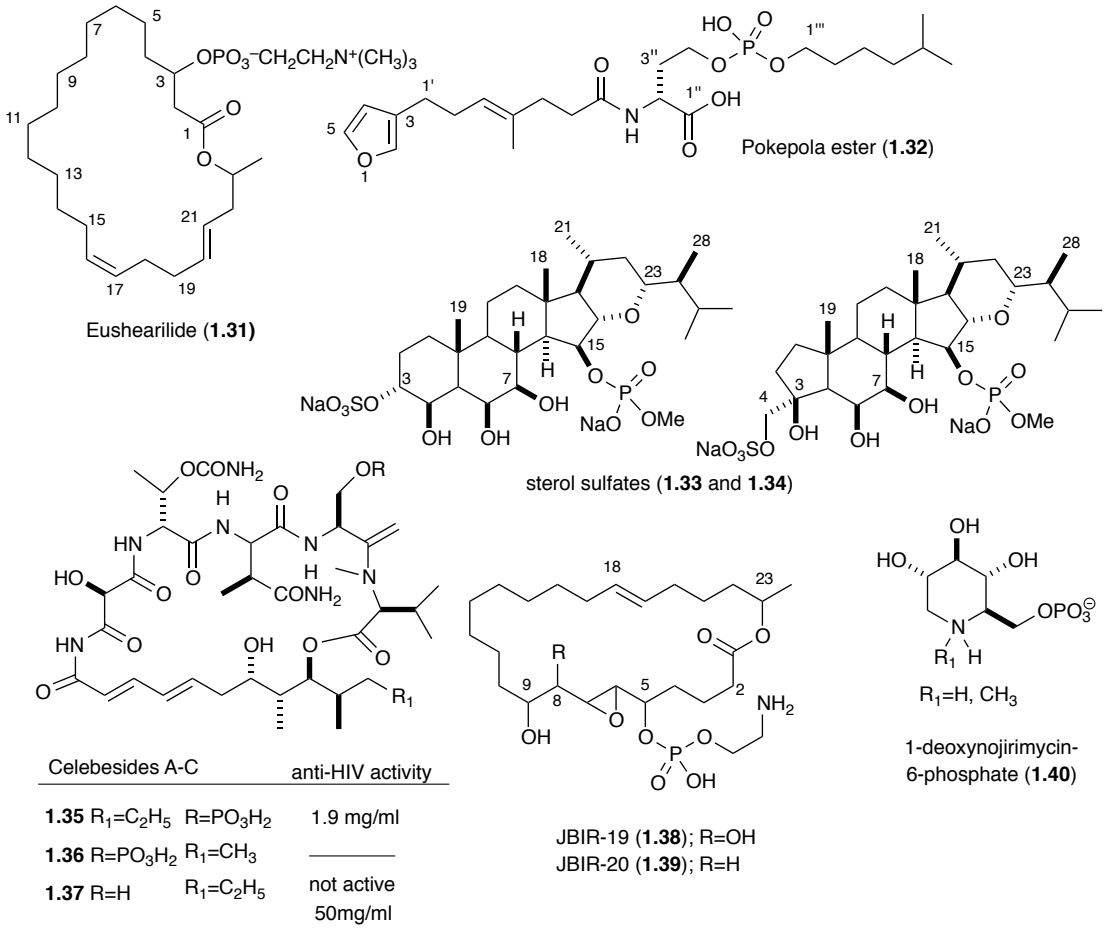
1.2.9. Phosphate-containing natural product that have not been synthesized

In addition to the above discussed molecules, there are several other phosphate-containing macrolides, as well as other phosphorylated marine natural products that have been reported (Figure 4). However, their respective syntheses have not been reported yet. Eushearilide (**1.31**), was isolated from *Eupenicillium shearii* IFM54447 in 2006 by Kawai and co-workers. This is the first report of a 24-membered macrolide antibiotic having the choline phosphate ester moiety as well as non-conjugated double bonds with no amino sugar moiety or hydroxyl groups on the ring structure.[30] Eushearilide exhibits antifungal activity against various fungi and yeasts, including human pathogens *Aspergillus fumigatus*, *Trichophyton* spp. and *Candida* spp.[30] JBIR-19 and JBIR-20 (**1.38** and **1.39**, respectively) are 24-membered macrolides isolated from the culture broth of the entomopathogenic fungus *Metarhizium* sp. fE61 that contains 2-aminoethyl phosphate esters and showed induced striking elongated morphology of *S. cerevisiae* at concentrations of 3.1 and 13 μM, respectively.[31]

Other phosphate-containing marine natural products include pokepola ester (**1.32**),[32] haplosamate steroids (**1.33** and **1.34**)[33] celebeside cyclic depsipeptides A–C (**1.35**–**1.36**)[34] and deoxynojirimycin derivatives (**1.40**).[35] Pokepola ester (**1.32**) is a diester of phosphoric acid isolated from Maui sponge *Sponigia oceania* in 1993 and exhibits mild anti-HIV activity.[32] Phosphorylated sterol sulfates **1.33** and **1.34** are isolated from marine sponge *Cribrochalina* sp. and shows metric metalloproteinase inhibition.[33] Celebesides A–C (**1.35**–**1.37**) are cyclic depsipeptides, isolated from *S.*

mirabilis sponge, possess the polyketide moiety and five amino acid residues, including an uncommon 3–carbamoyl threonine and a phosphoserine residue, which is present in celebesides A and B. Celebeside A (**1.35**) exhibit anti-HIV activity in a single-round infectivity assay with an IC_{50} value of 1.9 (0.4 μg/mL) while the non-phosphorylated analog celebeside C (**1.37**) was inactive at concentrations as high as 50 μg/mL.[34] In 2006, 1-deoxynojirimycin-6-phosphate (**1.40**) and its *N*-methyl derivative were isolated from the sponge *Lendenfeldia chondrodes*.[35] These are the

Figure 4: *Phosphate-containing natural product that have not been synthesized.*



first examples of phosphate derivative of 1-deoxynojirimycin (dNM) found in nature and its N-alkylated derivatives are known to be potent inhibitors of α-glucosidase.[36]

1.2.10 ***Limitations associated with phosphate-containing natural products***

The importance of phosphate as a key moiety in chemistry and biology is accentuated by the fact that nearly all known phosphate-containing natural products have been shown to possess potent biological activities, particularly within the realm of protein phosphatase inhibition. However, despite their potency, very few *in vivo* studies have been reported for phosphate-containing natural products, since their high inherent hydrophilicity imparts low bioavailability. The bioavailability issue of phosphates, is largely the consequence of the impermeability of phosphate anions to cell membranes at physiological pH ranges due to the inherent pKa's associated with phosphate diesters—which have a pKa of ~ 2, and phosphate monoesters—which have two pKa's of ~ 2 and ~7, respectively. Therefore, active transport is required for successful delivery of the phosphate-containing natural product into the cell. Furthermore, even though phosphates show remarkable stability to non-enzymatic hydrolysis, with half lives of hundreds years,[37] the large distribution of various phosphatases—which have the capability of removing the phosphate group—can hinder effective delivery into the cell of the "intact" phosphate-containing natural product.

A common strategy in medicinally active synthetic phosphate drugs—such as phosphate monoesters—is to increase their bioavailability by protecting them as phosphate triester prodrugs (prodrugs-*vide infra*) using easily removable groups.

However, to the best of our knowledge, this strategy has not been incorporated in phosphate-containing natural products.

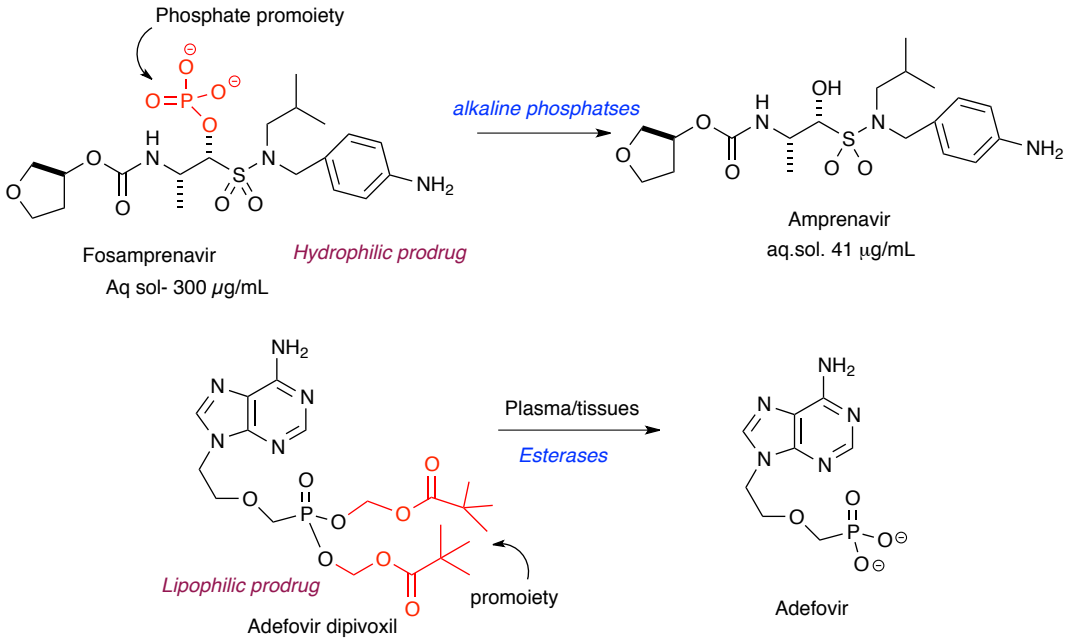
1.3 *Phosphate Prodrugs*

Prodrugs are bio-reversible substances of active drugs that can undergo *in vivo* enzymatic and/or chemical transformation to release the parent drug, which will participate in the desired action.[38] Prodrug strategies have become a useful tool in optimizing absorption, distribution, metabolism, and excretion (ADME) of drugs. However, these chemical modifications made, must be reversible which would allow the prodrug to convert back to parent drug *in vivo*, as well as it should be safe and rapidly excreted from the body.[39]

Phosphates are one such functional group (other functional groups: esters, carbonates, carbamates, *N*-Mannich bases, oximes, imines, amides, ethers) that the pharmaceutical industry has used to improve the bioavailability of active drugs.[40] There are several different ways that phosphates have been used in developing prodrug strategies (Figure 5).[40] As previously mentioned, due to the inherent pKa properties of phosphates at physiological pH, they carry either one or two negative charges. If a compound suffers from low bioavailability due to poor water solubility (i.e. compound has a high clogP), phosphate mono- or diesters have been strategically installed to improve water solubility (lower the clogP). In these cases, installation of an ionizable phosphate as a promoiety at the hydroxyl or amine functionalities will improve the water solubility for oral or parenteral delivery by making it more polar.[41] In addition, chemical stability, straightforward synthesis and rapid cleavage by

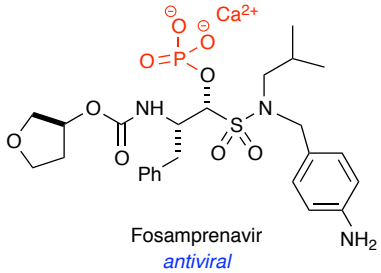
alkaline phosphatases are the added advantages with phosphates taken as a promoiety.[42]

Figure 5: *Role of phosphate in prodrug strategies.*

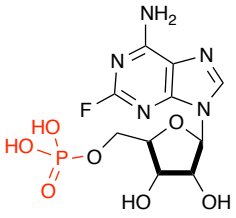


Fosamprenavir is a successful phosphate prodrug, which is used for treatment of HIV infection, and has an improved effect on oral delivery with the introduction of a polar phosphate group. This prodrug strategy reduces the dose to a 3 capsules twice-a-day dosage for fosamprenavir, to an 8 capsules twice-a-day dosage for the parent drug amprenavir.[43] Other examples for phosphate drugs, which are successful, are summarized in Figure 6.[38]

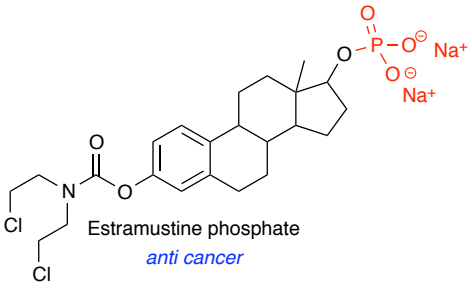
Figure 6: *Prodrugs employing a phosphate monoester as a promoiety.*



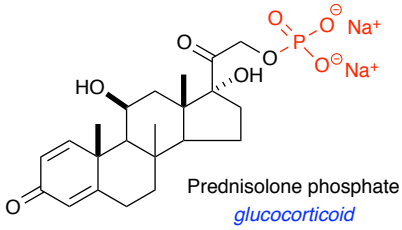
Fosamprenavir
antiviral
aq. sol. increased 10 fold



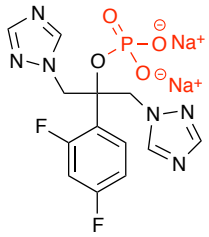
Fludarabine phosphate
antiviral



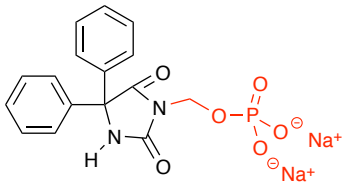
Estramustine phosphate
anti cancer



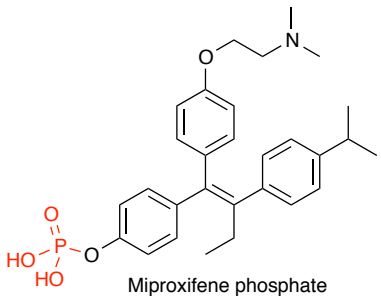
Prednisolone phosphate
glucocorticoid



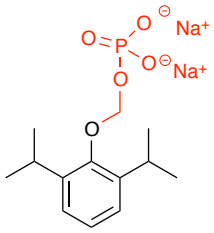
Fosfluconazole
antifungal
aq. sol. increased over 300 mg/ml



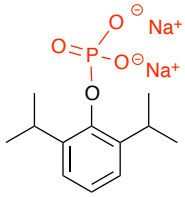
Fosphenytoin
anticonvulsant
aq. sol. increased from 20-25 μg/ml
to 140 mg/ml



Miproxifene phosphate
anti cancer
aq. sol. increased by 1000 fold



Phosphonooxymethyl propofol
anaesthetic
aq. sol. increased from 150 μg/ml
to 500 mg/ml



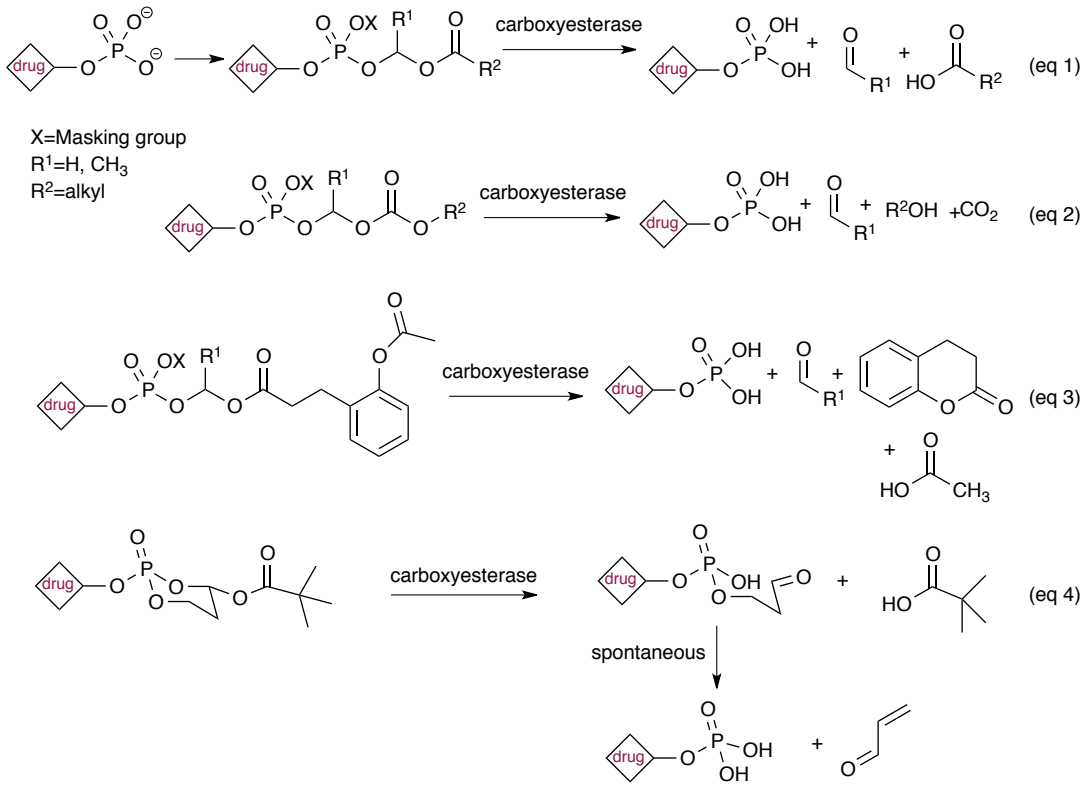
Propofol phosphate
anaesthetic
aq. sol. increased over 150 mg/ml

The second scenario is when a phosphate is an active component of the parent drug, the negatively charged phosphate group can present a significant problem in drug delivery, by imparting too much water solubility (i.e. too low of a clogP) or by succumbing to hydrolysis by alkaline phosphatase enzymatic reactions. In this latter case, efforts have been aimed at developing prodrug-containing, protected-phosphates

in the form of phosphate diesters or triesters in order to decrease water solubility [increase lipophilicity (i.e. raise the clogP)].[38,39] Moreover, since phosphate triesters are not common in nature—and enzymes that could cleave those triesters have not been reported—the issues with rapid alkaline phosphatase hydrolysis were circumvented by employing this protected-phosphate strategy. The most common strategy employed to mask phosphate dianion is conversion to phosphate triesters utilizing easily removable protecting groups such as acyloxyalkyl esters, S-acyl groups, and sulfidyl groups etc.

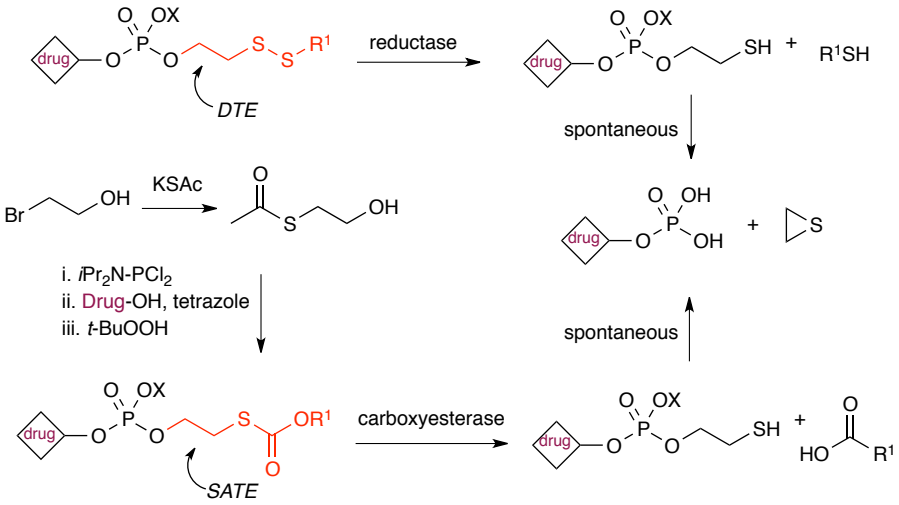
In the early 1980's, Farquhar and coworkers applied a protocol that has been used to mask the penicillin carboxy group in order to enhance its bioavailability, to mask phosphates with acyloxymethyl esters and after different masking approaches were reported.[44] Acyloxyalkyl esters were synthesized simply by alkylation of the phosphate with acyloxyalkyl halogenide in the presence of hindered base. Esters were cleaved through enzymatic hydrolysis and upon spontaneous hydrolysis of the resulting hydroxymethylene esters, the active parent drug was released [Figure 7, (eq 1)]. Prodrugs of ACE inhibitor fosinopril and antiviral compound (*R*)-9-([phosphonomethoxy]propyl)adenine (PMPA) were synthesized utilizing alkoxycarbonyloxyalkyl groups to control the elimination of formaldehyde and carboxylic acids during the hydrolysis (eq 2).[45] In addition, 4-acetoxybenzyl esters, α-acyloxyalkyl esters, and acetoxy-phenyl esters and cyclic phosphates have been successfully utilized as masking groups (Figure 7).[46]

Figure 7: *Different approaches to phosphate triester prodrugs.*



A variety of esterase-labile thioesters have also been employed in prodrug strategies. As enzymatically removable moieties, *S*-acylthioethyl (SATE) esters or *S*-[(2-hydroxyethyl)-sulfidyl]-2-thioethyl (DTE) esters have been utilized in masking antiviral nucleoside monophosphates and phosphonates (Figure 8).[47] The active drug with the monophosphate was released by enzymatic cleavage followed by spontaneous elimination of thiirane. However, further development was limited due to the associated toxicity risk with the byproduct ethylene sulfide.[39]

Figure 8: *Prodrugs of phosphate triesters with sulfidyl and S-acyl groups.*



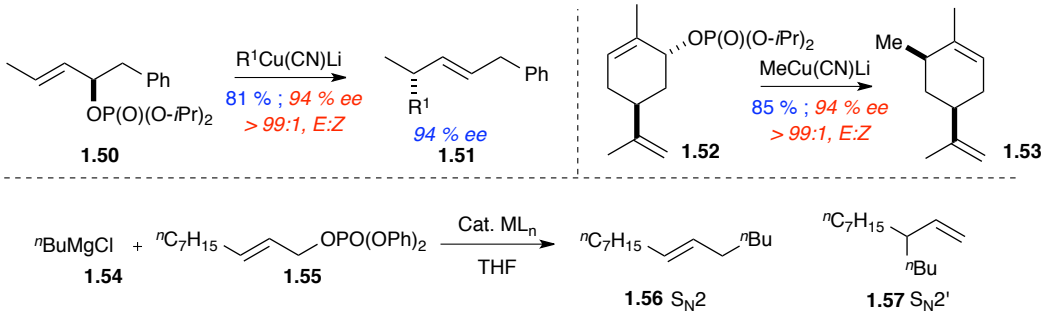
1.3. Use of phosphates in synthesis

In addition to the promising role in biochemistry, phosphates are also useful tools in synthetic chemistry. Due to the lower reactivity of phosphates esters, halides and sulfonates are preferred in nucleophilic substitution reactions over phosphates. However, the leaving group ability of phosphates, coupled with their electrophilic nature, multipodal coupling abilities—and orthogonal selective cleavage profiles using acid, base or reductive condition—impart a unique and impressive portfolio of reactivity that have allowed them to emerge as viable intermediates in synthesis. In this regard, several recent reports have shown impressive synthetic applications of phosphates, including their use in allylic substitution,[48] reductive cyclizations,[49] phosphate extension reactions/iodolactonization,[50] transition metal-mediated cross coupling reactions,[51] and temporary tether-mediated, one-pot sequential processes.

1.3.1. Allylic phosphates

There are several reports published on different substitution reactions of allyl phosphates depending on the nature of the nucleophile and the catalyst. In 1958, it was first reported that soft bases (PhS^-, I^-, CN^-) attack at alkyl group of alkyl phosphates showing clean S_N2 displacement reaction, while hard bases (NaOMe and alkyllithium) attack the phosphorus atom.[52] In 1991, Yamamoto and co-workers demonstrated the superiority of phosphates as leaving groups in comparison to chlorides and mesylate in a seminal copper-mediated *anti*-S_N2' displacement reaction of secondary allylic phosphate **1.50**, affording allylic substituted product **1.51** in high *E:Z* selectivity while maintaining the excellent chirality transfer with 94% enantiomeric excess (Scheme 11).[53] However, addition of a Grignard reagent into an allylic phosphate in the presence of Fe- and Ni-based catalysts [$Fe(acac)_3$, $NiBr_2$]

Scheme 11

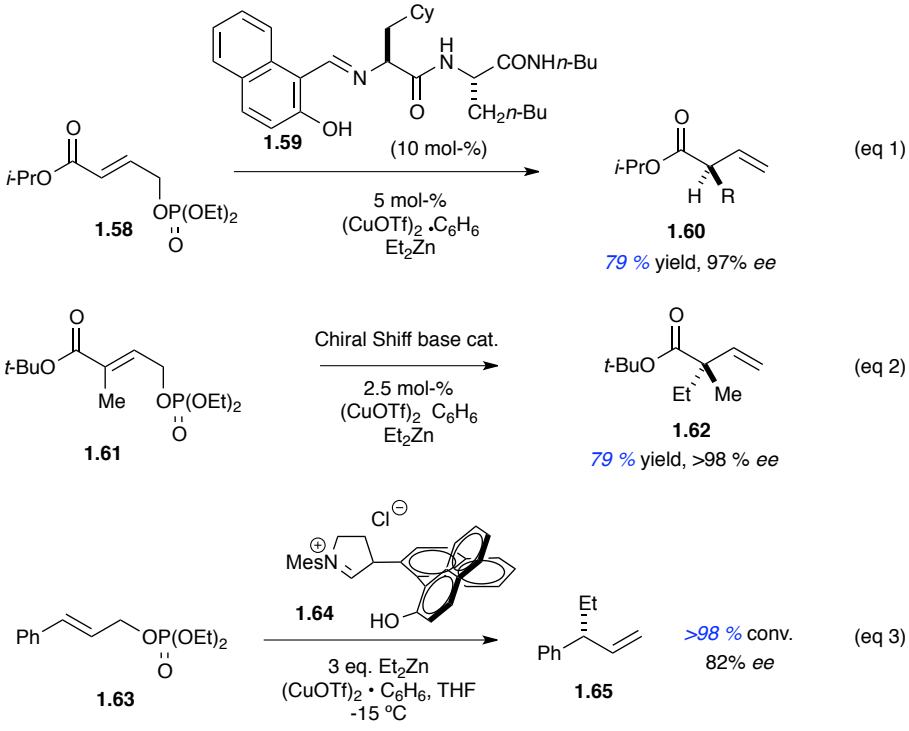


Cat. ML_n	*Conditions*	*Yield %*	S_N2:S_N2'
None	0 °C, 6 h	32	91:9
$Fe(acac)_3$	- 76 °C, 1h	94	99:1
$NiBr_2$	- 73 °C, 2h	93	>99:1
CuCN•2LiCl	- 76 °C, 1h	98	1:99

resulted in S_N2 displacement instead of exclusive S_N2' displacement reaction which was observed with Cu(I) catalyst (CuCN•2LiCl) (Scheme 11).[54] In 2001, Chong and coworkers, and in 2003, Knochel and coworkers also reported similar observations in acyclic and cyclic allylic phosphate displacement reactions.[55]

Asymmetric variants of allylic displacement reactions via an *anti*–S_N2' pathway with chiral Schiff bases, BINAP and an *N*-heterocyclic carbene have also been reported (Scheme 12 and 13). In 2004, Hoveyda and co-workers reported the Cu-catalyzed asymmetric alkylation of unsaturated esters bearing a primary γ-phosphate with alkyl zinc in the presence of peptidic Schiff base **1.59** and application of this protocol in the synthesis of topoisomerase II inhibitor (*R*)-elenic acid.[56] In addition, application of the same protocol in the synthesis of quaternary all-

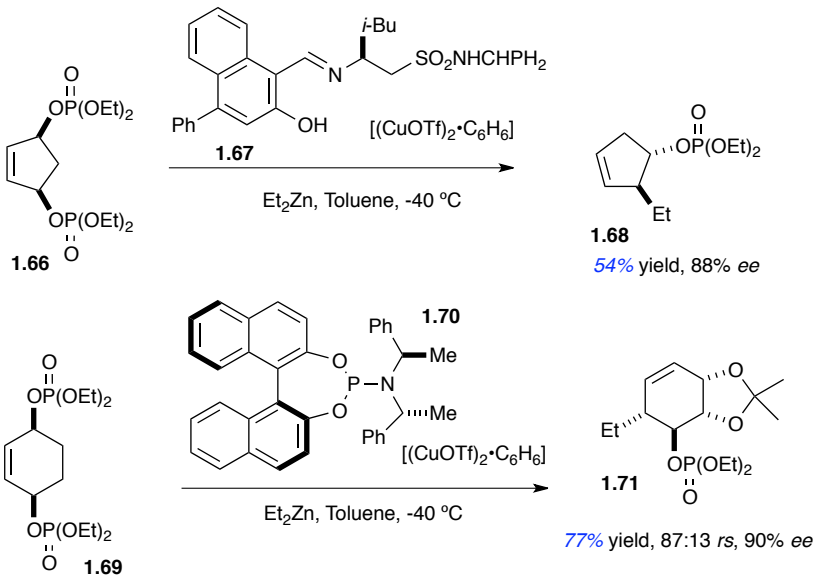
Scheme 12



carbon stereocenters in high yield, as well as high regio- and enantioselectivities, were also reported.

In 2003, Gennari and co-workers disclosed another application of the enantioselective Cu-catalyzed organo-zinc addition in the presence of chiral, non-racemic Schiff reagents (**1.67** and **1.70**) in a highly regio-, diastereo-, and enantioselective desymmetrization of the *meso*, cyclic allylic *bis*-diethylphosphates **1.66** and **1.69** (Scheme 13).[57a]

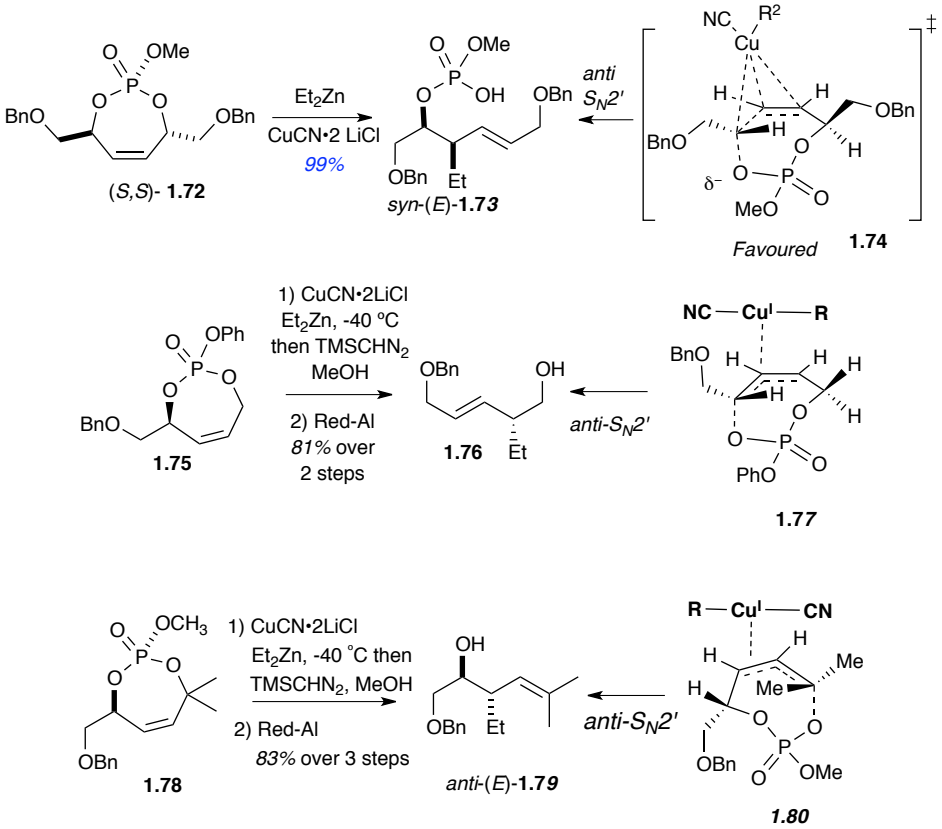
Scheme 13



In 2006, Hanson and coworkers reported the desymmetrization of the *pseudo*-C_2-symmetric cyclic phosphate **1.72** via an *anti*-S_N2' Cu–mediated allylic phosphate displacement, which afforded the *syn*-(*E*)-phosphate **1.73** as a single diastereomer (Scheme 14).[58] According to the proposed transition state **1.74**, observed excellent diasteroselectivity was dictated by allylic $A^{1,3}$-strain from the CH_2OBn-side chain,

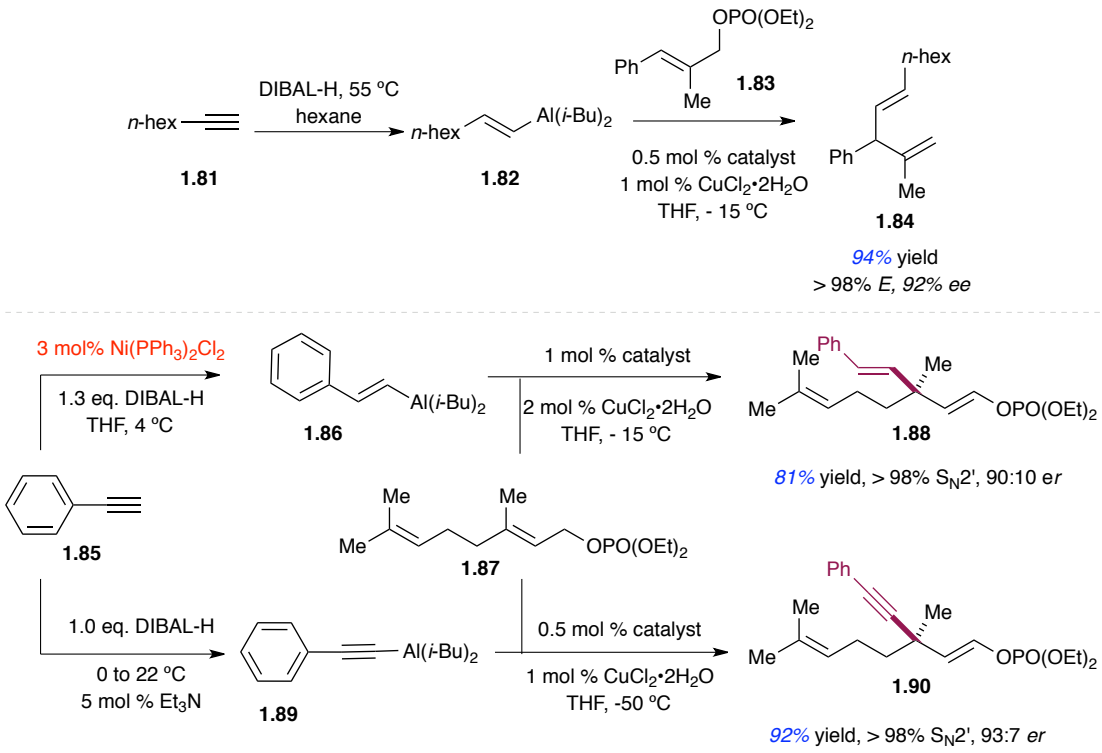
which is less prominent in **1.74**, allowing proper alignment of σ* and π* orbitals with approaching cuprates. However, with asymmetric cyclic phosphates, the electronic bias of more labile phosphate (secondary in **1.75** and tertiary in **1.78**) leaving group determined the higher regioselectivity obtained in allylic displacement with cuprates. After removal of primary phosphate with Red-Al®, chiral, non-racemic homoallylic alcohol *anti*-(*E*)-**1.79** was obtained in good yield.

Scheme 14



In addition to organo-zinc and Grignard reagents, alkyl aluminum reagents[59] as well as alkyl boron reagents[60] were also utilized in asymmetric Cu-catalyzed allylic displacement reactions of allyl phosphates. In 2008, Hoveyda and co-workers reported the asymmetric, Cu-catalyzed S_N2' displacement reaction with *in situ* prepared vinyl aluminum reagents **1.82** to synthesize 1,4-dienes **1.84** on gram-scale (Scheme 15). Furthermore, synthesis of all carbon quaternary centers was also accomplished via enantioselective allyl substitution of allyl phosphates with vinyl aluminum reagents or propargyl aluminum reagents in the presence of sulfonate–bearing, chiral, bidentate *N*-heterocyclic carbene (NHC) complexes.[59] The aryl-,

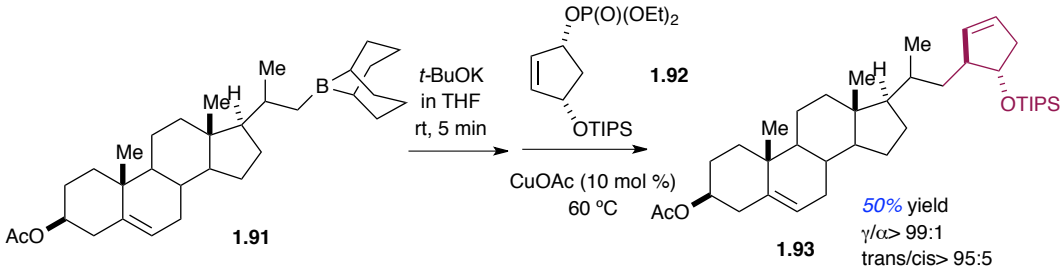
Scheme 15

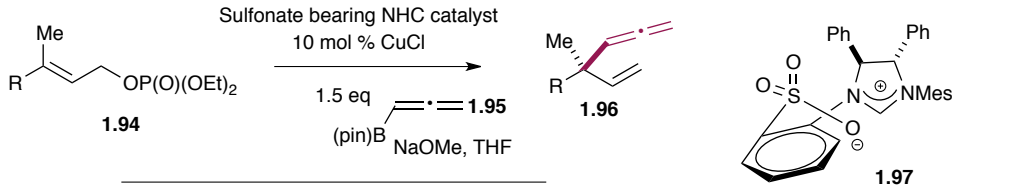


vinyl-substituted aluminum reagents **1.86**, which are difficult to synthesize with DIBAL-H, were prepared employing Ni-catalyzed hydroalumination.[61]

In 2010, Sawamura and co-workers described a highly regio- and stereo-selective Cu-catalyzed allylic substitution of acyclic and cyclopentane-diol-based allylic phosphates with alkyl boranes.[60] Notably, these couplings proceeded with excellent γ- and *E*-selectivities and preferential 1,3-*anti* selectivity and the synthetic utility of this route was demonstrated in the synthesis of steroid derivative **1.93** (Scheme 16). The additional advantages of this protocol included facile preparation of boryl compounds via hydroboration of olefin and functional group tolerability. Several other groups have also reported the synthetic utility of alkyl/aryl borane and

Scheme 16



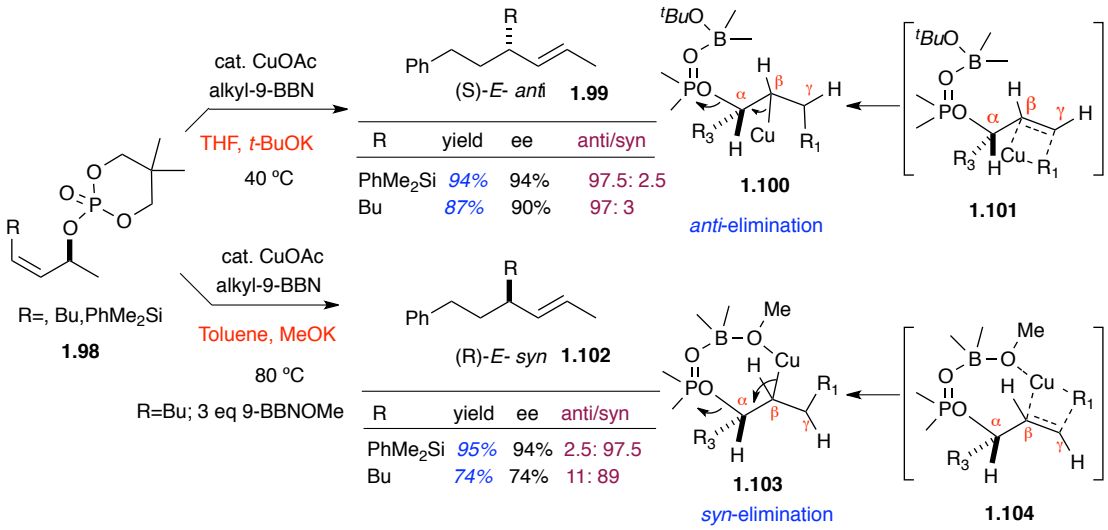


R	conv (%): yield (%)	$S_N2':S_N2$
Ph	89:74	>98:2
Cy	>98:72	>98:2
p-ClC_6H_4	85:77	>98:2
m-BrC_6H_4	82:72	>98:2
o-$MeOC_6H_4$	>98:83	>98:2

allyl phosphate couplings.[60] In 2012, Hoveyda and co-workers described the chiral NHC-Cu-**1.97**-catalyzed, enantio- and regio-selective, allylic substitution reaction with allene borane **1.95** and allylic phosphate **1.94**. Allene-bearing tertiary or quaternary carbon stereogenic centers were generated with excellent yield (95%), enantiomeric ratio (99:1), and S_N2' selectivity (> 98 %, Scheme 16).

In 2012, Sawamura's group further illustrated that the stereochemical outcome of the Cu-catalyzed coupling reactions of an alkyl borane and chiral allylic phosphate can be switched from 1,3-*anti* to 1,3-s*yn* by varying the reaction conditions (Scheme 17).[60] When a bulky alkoxide (t-BuOK) and a polar solvent such as THF were employed, the coupling proceeded with *anti*-selectivity to provide product **1.99** in excellent yield (85–95%). However, when less sterically demanding MeOK and a non-polar solvent (toluene) were used, the reaction proceeded with *syn*-selectivity to generate **1.102** in high yield. Mechanistic studies revealed that Cu-catalyzed allyl-

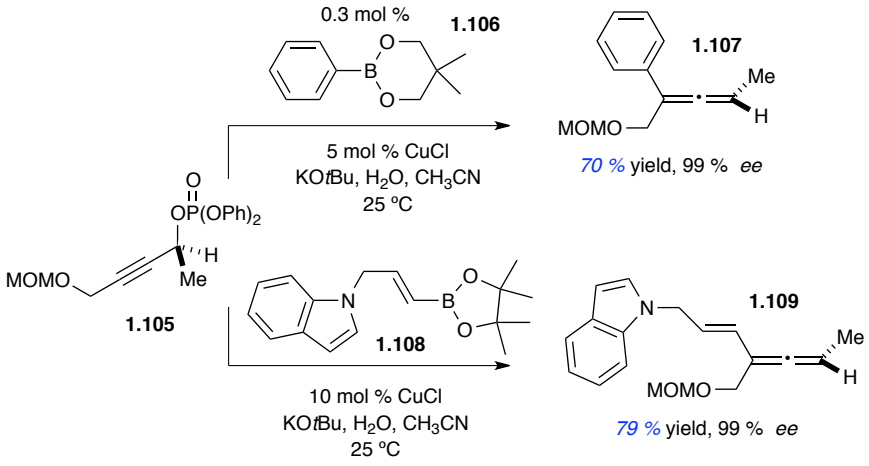
Scheme 17



alkyl coupling reactions operate via the addition–elimination mechanism of neutral organo copper reagents to provide excellent γ-selectivity. When a bulky alkoxide was utilized, *anti*-addition followed by *anti*-elimination resulted. Conversely, the use of a sterically less-hindered alkoxide afforded *syn*-addition of the alkyl copper complex with overall *syn*-stereochemistry with respect to the leaving group; subsequently *syn*-elimination provided stereochemically reversible products (Scheme 17).

Propargyl phosphates were also employed in Cu-catalyzed coupling reactions with aryl-or alkenyl-boronates to synthesize aryl- and alkenyl-conjugated allenes (Scheme 18).[62] The reaction of enantiomerically pure propargylic phosphates showed excellent point-to-axial chirality transfer with *anti* stereochemistry to provide axially chiral conjugated allenes.

Scheme 18



In addition to the above-mentioned, Cu-catalyzed allylic alkylations, allylic phosphates have been used in Pd-mediated alkylation reactions as well.[63]

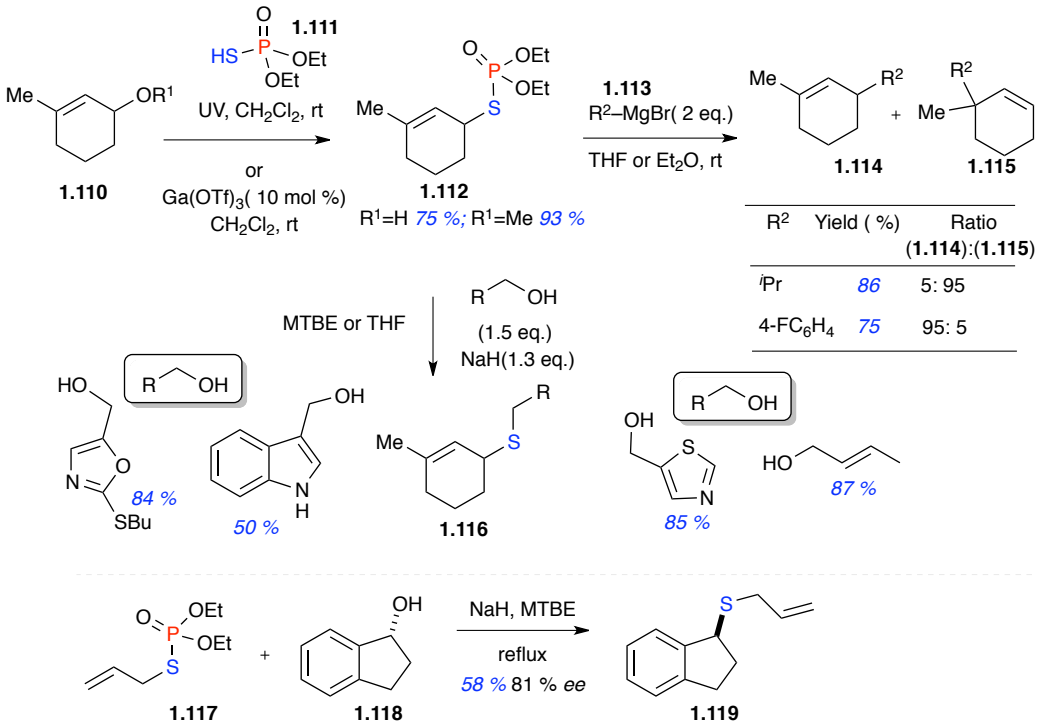
1.3.2. Thiophosphates:

Thiophosphates have also been utilized in variety of synthetic strategies, including allylic substitution reactions, allylic fluorination reactions, as well as surrogates for H_2S. In 2010, Wu and coworkers reported transition-metal-free allylic displacement reactions of cyclic and acyclic allylic phosphothioates **1.112** with Grignard reagents. These thiophosphates were synthesized employing photochemically-promoted substitution of alcohols **1.110** with phosphorothioic acids **1.111**, which can be synthesized in multi-gram scale with diethyl phosphite and S_8 (Scheme 72).[64] However, this thiolation reaction occurred only with allylic alcohols, such as **1.110**. Primary, secondary, and tertiary aliphatic alcohols as well as benzyl alcohols did not provide the desired thiophosphates. Despite this limitation, un-catalyzed alkylation reactions (Grignard addition) were shown to be broadly applicable to a wide range of nucleophiles and tolerant of both electron-withdrawing and donating groups as well as vinylic substrates. Moreover, both primary and secondary alkyl Grignard reagents also participate in the substitution reaction. Interestingly, aromatic and alkenyl nucleophiles underwent the S_N2–type displacement to provide **1.114** selectively; whereas, secondary aliphatic Grignard reagents provide the S_N2'-type displacement product **1.115** as the major product. To circumvent the limitation of the above-discussed thiolation reaction, $Ga(OTf)_3$-catalyzed direct displacement reaction of alcohols with sulfur nucleophiles were developed and it possessed greater substrate scope to include a larger variety of alcohol starting materials.[65] However, although tertiary alcohols were smoothly

converted to their corresponding thiophosphates, allylic or aromatic substitution is required for the reaction to proceed with secondary and primary alcohols.

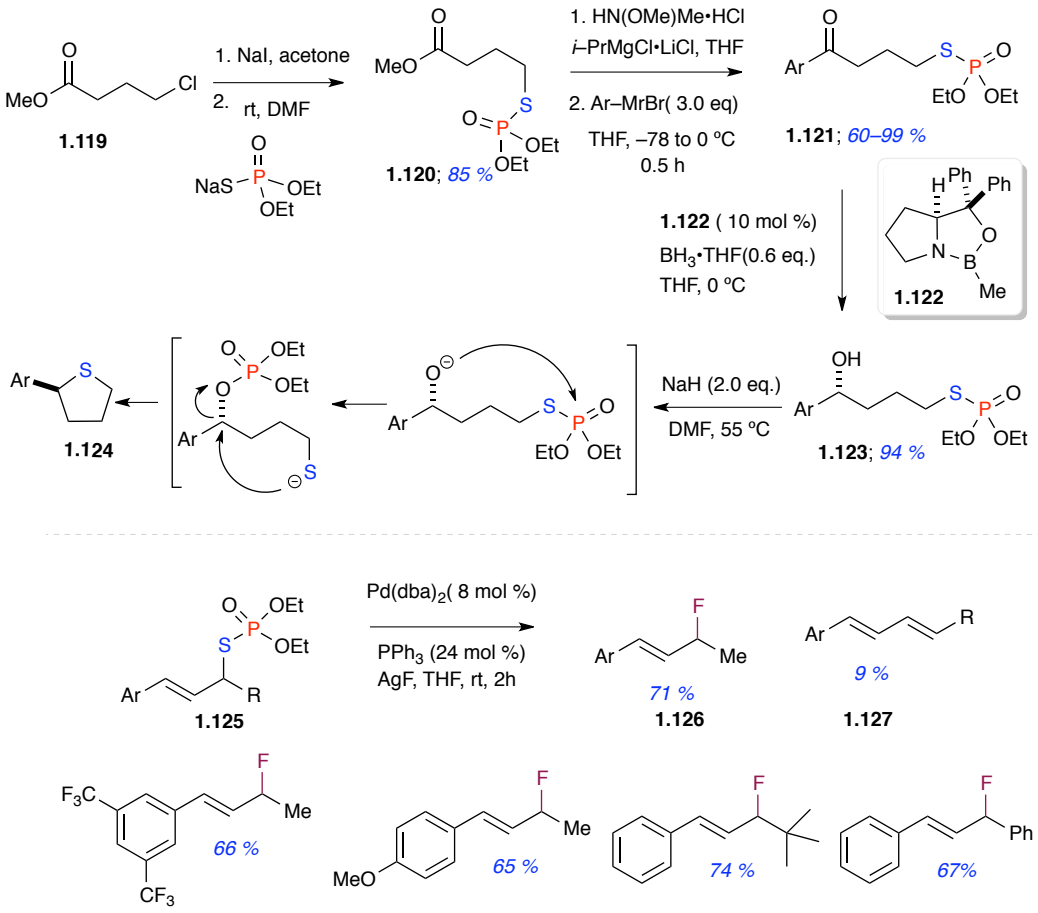
Another application of thiophosphate is the synthesis of thioethers via direct coupling of phosphorothioate ester **1.112** with an appropriate alkoxide, generated by treatment with NaH in THF (Scheme 19). Most notably, this protocol is compatible with substrates containing a series of potentially sensitive functionalities, including nitriles, esters, and unprotected indole nitrogens, as well as a wide range of nitrogen-, oxygen-, and sulfur-containing heterocycles. Wu and coworkers further illustrated the application of phosphorothioate ester **1.117** in the synthesis of chiral, non-racemic thioethers **1.119** with overall inversion of stereochemistry from **1.118** (Scheme 19).[66]

Scheme 19



In 2012, Wu and coworkers reported two additional applications of thiophosphates: (i) as H_2S surrogates in synthesis of chiral tetrahydrothiophenes **1.124**, and (ii) Pd-catalyzed allylic fluorination in the synthesis of allylic, fluoro compound **1.126** (Scheme 20).[67] The key reaction involved in the synthesis of tetrahydrothiophenes is the base-promoted, intra-molecular, carbon–sulfur bond formation that was obtained through a highly stereospecific double S_N2 displacement mechanism. Thiophosphate **1.120** was obtained from an iodoester intermediate, which was obtained from corresponding chloroester **1.119** via the alkylation of a phosphorothioic acid precursor. Weinreb amide formation followed by Grignard addition, afforded keto thioesters **1.121** in good to excellent yield. Asymmetric reduction of **1.121** with Corey-Bakshi-Shibata catalyst **1.122** provided the cyclization precursor **1.123**, which, upon treatment with NaH, afforded the tetrahydrothiophenes **1.124** in excellent yields. In the synthesis of allylic fluoro- compounds, AgF was used as the "F^-" source and mechanistic investigations revealed that the reactions are stereospecific and proceeds through a Pd π-allyl intermediate resulting in complete retention of stereochemical configuration in the corresponding fluorinated products.

Scheme 20



1.3.3. Enol phosphates (vinyl phosphates)

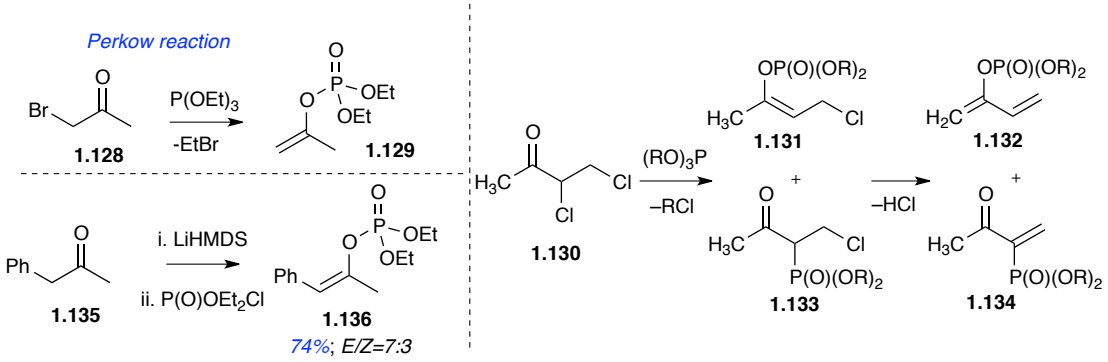
Enol phosphates represent another versatile phosphate-based synthetic intermediate that has been heavily utilized in organic synthesis, namely in metal-catalyzed cross-coupling reactions. Their widespread use is due to their greater stability, cost effectiveness, and benign chemistry when compared to their triflate counterparts, as well as a number of methods for their efficient synthesis.[68,69] The chemistry and properties of enol phosphates was first reviewed in 1961.[70] Since then,

several methods for the synthesis, as well as reactions of enol phosphates have been reported, some of which are summarized below.

1.3.3.1. Synthesis of enol phosphates

The earliest reported protocol for enol phosphate formation is the reaction of α-haloketones **1.128** with trialkyl phosphites from the seminal studies, by Michaelis, Arbuzov and Perkow.[71] In a related variant, Rosen and coworkers reported the reaction of di-halo-compound **1.30** (3,4-dichlorobutanone) with trialkyl phosphites, which resulted in a mixture of dialkyl enol phosphate **1.133** as the major product, and phosphonate esters **1.134** (Scheme 21).[72] However, greater utilization of this protocol was limited due to lack of commercial sources as well as the difficulties in synthesizing the required α-haloketone.

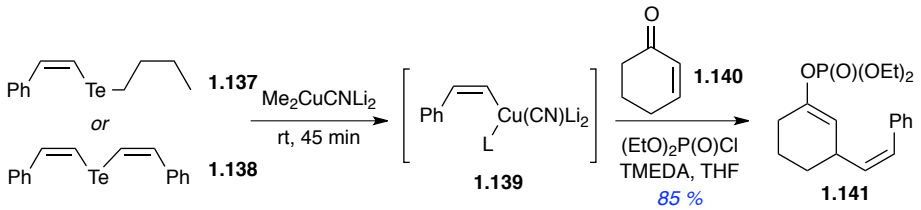
Scheme 21



The most common method to generate enol phosphates involves the treatment of ketones/aldehydes **1.135** with an appropriate base to allow for the trapping of the resulting enolate with a suitable phosphorus electrophile, most commonly a dialkyl phosphorochloridates (Scheme 21).[73]

In 2000, Comasseto and coworkers reported the formation of *Z*-vinylic cyanocuprates **1.139** via the transmetallation reaction between *Z*-vinylic tellurides **1.137** and **1.138** and higher order cyanocuprates (Scheme 61).[74] Subsequent conjugate addition of the cuprates to enone **1.140**, followed by trapping of the resultant enolate via *O*-phosporylation, and afforded enol phosphate **1.141** in excellent yield.

Scheme 22

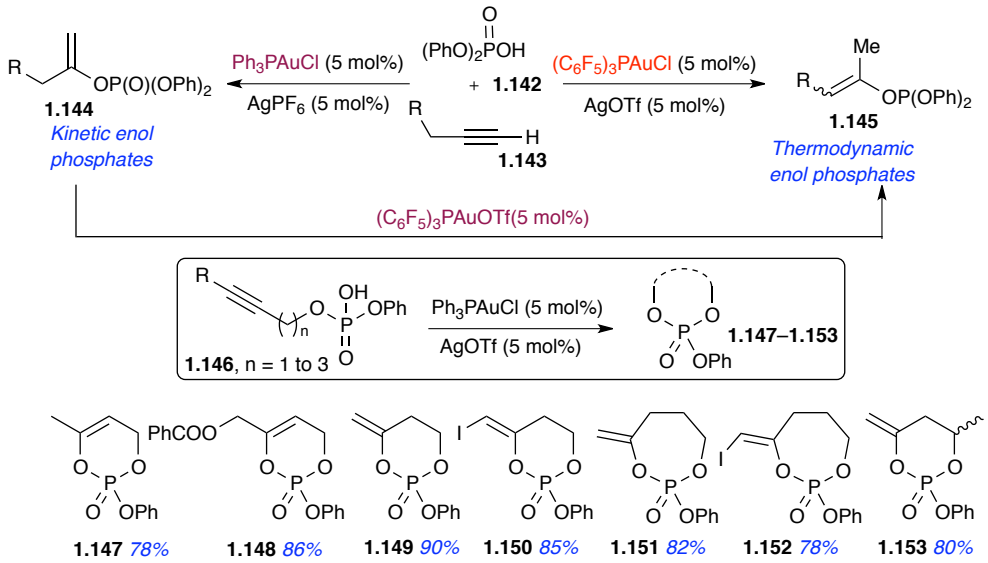


Even though, kinetically controlled enolization can be achieved very effectively with the above mentioned trapping strategy, the synthesis of thermodynamically favored more substituted enol phosphorus compounds is rather challenging. Thus several other methods have been developed to synthesize the thermodynamically favored enol phosphates with high selectivity.

In 2010, Lee, Kim and coworkers developed a catalytic hydrophosphoryloxylation of alkynes using diphenyl phosphate [$(PhO)_2P(O)OH$], where ligand-specific Au(I)-catalysis resulted in selective formation of either the kinetic or thermodynamic enol phosphate (Scheme 23).[75] The kinetic enol phosphate was exclusively afforded with $[Ph_3PAuCl]/AgPF_6$ while the catalyst $[(C_6F_5)_3PAuCl]/AgOTf$ provided the thermodynamically favored enol phosphate

with high selectivity. In addition, conversion of kinetic enol phosphates **1.144** (generated by the reaction of phosphate **1.142** with alkyne **1.143**) to thermodynamic enol phosphates **1.145** was also accomplished with catalyst $(C_6F_5)_3PAuOTf$. In 2011, the same group synthesized alkynyl hydrogen phosphates **1.146** by the treatment of alkynols with phosphorodichloridate.[76] These alkynyl hydrogen phosphates underwent 6-*endo-dig*, 6-*exo-dig*, or 7-*exo-dig* cyclization in the presence of a Au(I) catalyst to furnish 6- and 7-membered cyclic enol phosphates **1.147–1.153** in good to excellent yields.

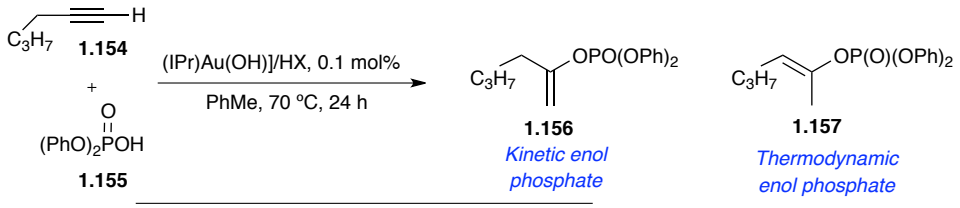
Scheme 23



In 2012, Nolan and coworkers reported a Ag-free synthesis of alkenyl enol phosphates **1.156** from alkyne **1.154** and diphenylphosphate diesters **1.155** with high selectivity by cationic Au(I) complexes generated *in situ* from the pre-catalyst[(IPr)Au(OH)] and Bronsted acid (HX) (Scheme 24).[77] The selectivity for the kinetic or the thermodynamic alkenyl phosphates is dependent on the nature of X.

When TfOH was employed thermodynamic vinyl phosphate **1.157** resulted with high selectivity (92:8), whereas, for kinetic enol phosphate **1.156** complete selectivity was achieved with HBF_4.

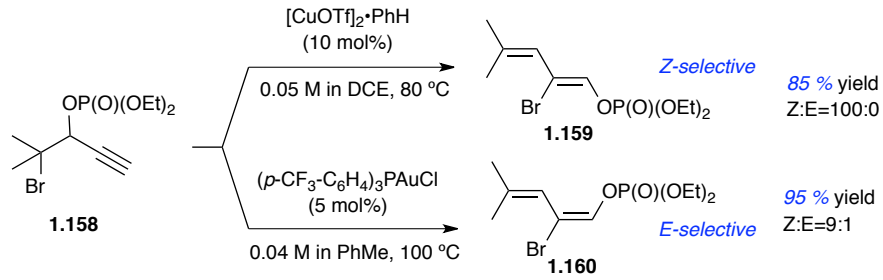
Scheme 24



HX	Kinetic/Thermodynamic	Conv. (%)
TfOH	8: 92	100
HBF_4	1:0	100

In 2012, Gevorgyan and coworkers reported the use of Cu- or Au-catalysis in a selective migratory cascade reaction with α-halogen-substituted propargylic phosphates **1.158** to generate highly functionalized 1,3-dienes (Scheme 25).[78] Occurring through either of two catalytic pathways (Cu- or Au-mediated), this stereo-

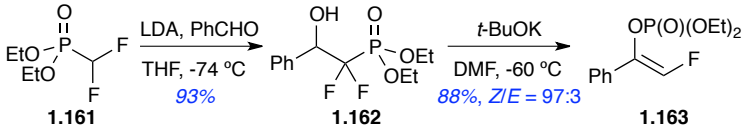
Scheme 25



divergent method allowed the generation of both (*Z*)-**1.159** and the (*E*)-1,3-dienes **1.60** from propargylic phosphates **1.158**. Thus (*E*)-dienes was provided exclusively with a gold catalyst while a copper catalyst afforded (*Z*)-dienes predominately.

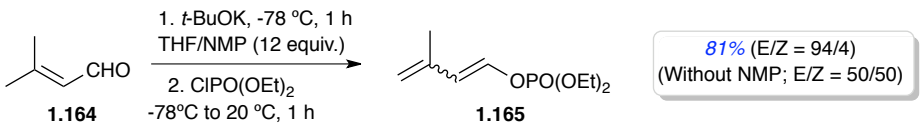
In 2009, Beier and coworkers utilized the phosphorus-Brook rearrangement of difluorophosphonate **1.162** in the synthesis of (*Z*)-fluoro-enol phosphate **1.163** (Scheme 26). [79] Aldol coupling of difluoromethylphosphonate **1.161** and benzaldehyde, in the presence of LDA, generated intermediate **1.162**, which, upon alkoxide formation with *t*BuOK, underwent a [1,4]-phosphorus-Brook rearrangement to yield (*Z*)-fluoro-enol phosphate **1.163** in excellent yield and selectivity.

Scheme 26



In 2008, Gager and coworkers demonstrated the first stereoselective method of preparation of (*E*)-dienol phosphates **1.165** from unsaturated aldehydes such as **1.164**, via the stereoselective enolization of a conjugated alkenal by *t*BuOK in the presence of *N*-methylpyrrolidinone (NMP) (Scheme 27).[80]

Scheme 27

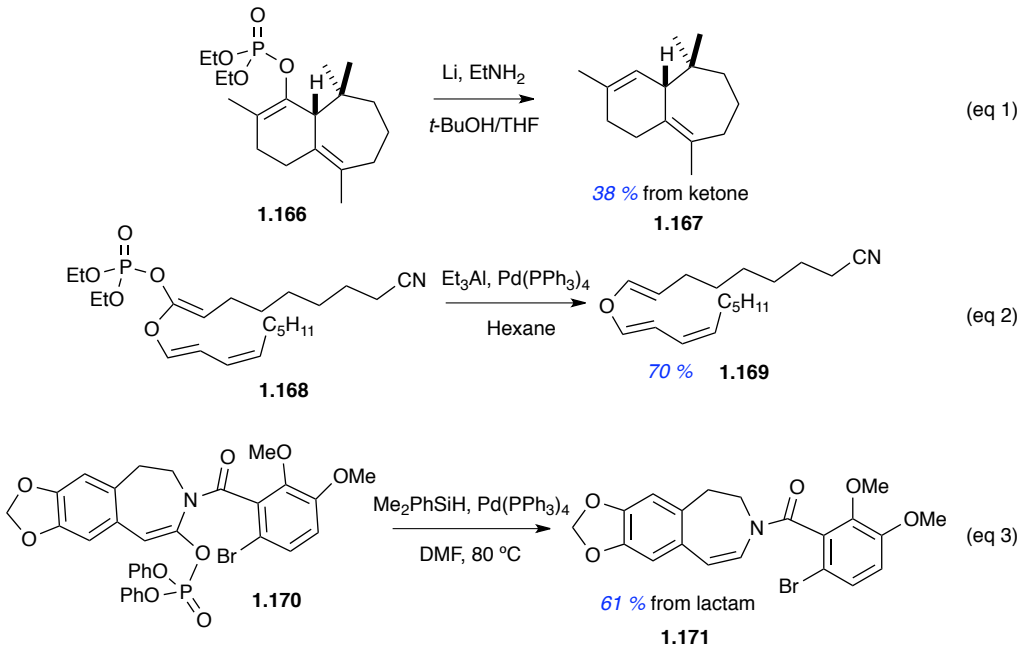


1.3.3.2. Reactions of enol phosphates

As previously mentioned, the synthesis of enol phosphates has gained prominence due to their application in a wide range of cross coupling reactions (such as Stille, Suzuki-Miyaura, Negishi, Kumada, Sonogashira, and Mizoroki-Heck reactions) en route to complex synthesis.[68] In particular, the Pd-catalyzed synthesis of *N*- and *O*-heterocycles from enol phosphate precursors has emerged as a significant faction in the realm of Pd-couplings and was highlighted in a recent review.[69] In addition, enol phosphates are more stable than their enol triflate counterparts, which tend to be expensive, corrosive, and more robust than their silyl-ether analogs, which are, in general, more sensitive to a variety of reaction conditions. Thus, enol phosphates have emerged as useful alternatives to traditional protecting/trapping groups in reactions that incorporate the use/generation of carbon enolates.

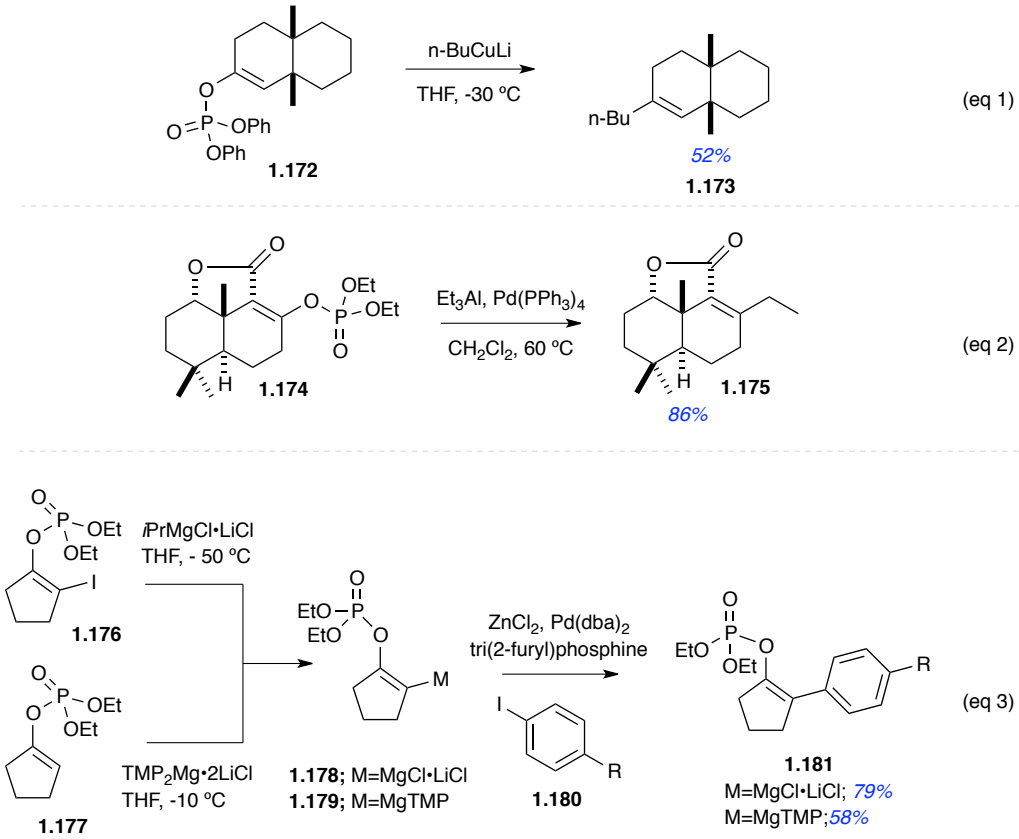
In 1969, Ireland and coworkers reported the first synthetic use of enol phosphates in their synthesis of alkene **1.167** from the ketone-derived enol phosphate **1.166** under reductive conditions using Li/$EtNH_2$ in *t*-BuOH (Scheme 28).[81] Since then, a number of reductive variants were developed, including $Et_3Al/Pd(PPh_3)_4$ (eq 2), and classical hydrogen transfer conditions such as HCOOH in the presence of silanes (eq. 3, Scheme 28).[82]

Scheme 28



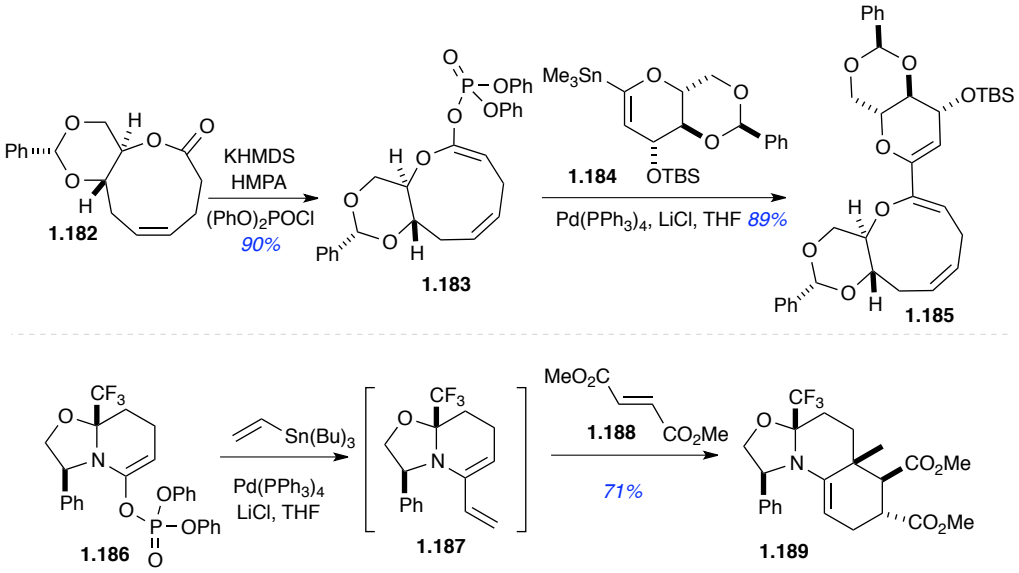
In 1976, Blaszak and coworkers were the first to demonstrate the conversion of enol phosphates to substituted alkenes using organo cuprates (RCuLi) (eq 1; Scheme 29).[83] Seminal reports by Oshima and coworkers followed and showed that Pd-mediated alkylation with trialkyl aluminum reagents provided better chemoselectivity as well as stereocontrol (eq 2).[84] Utilization of BBN derivatives, zinc reagents and alkyl Grignard reagents (with iron catalysts) have provided the solution for β-hydride elimination that sometimes hampers use of trialkyl aluminum reagents.[85] Recently Knochel and co-workers showed that, tetra-substituted enol phosphates **1.181** can be synthesized via alkylation of the magnesiated enol phosphate derivatives **1.178** and **1.179** derived from enol phosphate **1.177** and α-halo enol phosphate **1.176**.[86]

Scheme 29



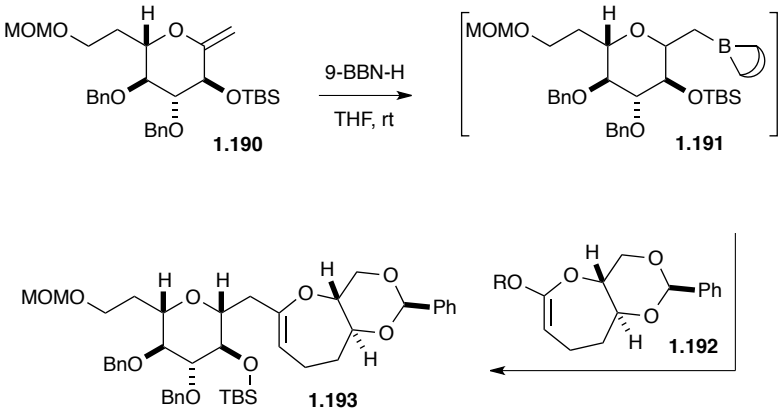
In 1997, Nicolaou and coworkers reported the first example of Pd-mediated cross coupling reactions of enol phosphates with vinyl organometallic reagents en route to the synthesis of functionalized cyclic enol ethers (Scheme 30).[51] Enol phosphate **1.183** was synthesized from lactone **1.182** utilizing KHMDS, HMPA and $(PhO)_2POCl$. Subsequent Stille coupling with stannane **1.184** provided cyclic enol ether **1.185** in 89% yield. In addition, a series of enol phosphates derived from ketones, oxazines, pyrazines and lactams was utilized in Stille couplings with vinylstannanes to provide the corresponding dienes (Scheme 30).[87]

Scheme 30



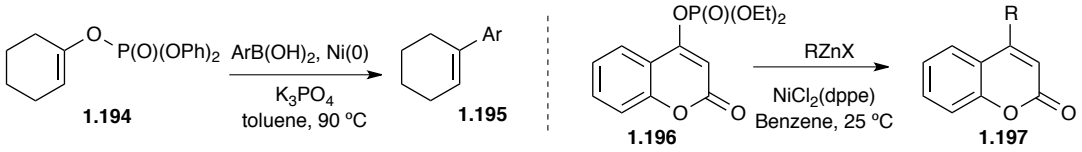
In 1999, Sasaki and coworkers demonstrated that enol phosphates [R = $P(O)(OPh)_2$] were superior to enol triflates (R = SO_2CF_3) in the Suzuki–Miyaura coupling between alkylborane **1.191** (synthesized from hydroboration of alkene **1.190**) and the enolic compound **1.192** en route to the enol ether subunit **1.193** (Scheme 31).[88] Utilizing the same conditions in the Suzuki–Miyaura coupling of a variety of medium-sized cyclic enol phosphates (6- to 9-membered), the authors completed the synthesis of the ABCD-ring fragment of the natural product CTX3C.

Scheme 31



In 1999, Yang and Nan reported the first utilization of cyclohexenylphosphate **1.194** in the Ni(0)-catalyzed Suzuki cross-coupling reaction with various aryl boronic acids to furnish coupled products **1.195** (Scheme 32).[89] In 2001, Yang and Wu described the Ni-catalyzed Negishi cross-couplings of 4-diethylphosphonooxycoumarins **1.196** with a variety of organozinc reagents to generate 4-substituted coumarins **1.197** at room temperature.[90] The yields are generally high for arylzinc halides, although alkylzinc bromides generated product in only moderate yields.

Scheme 32

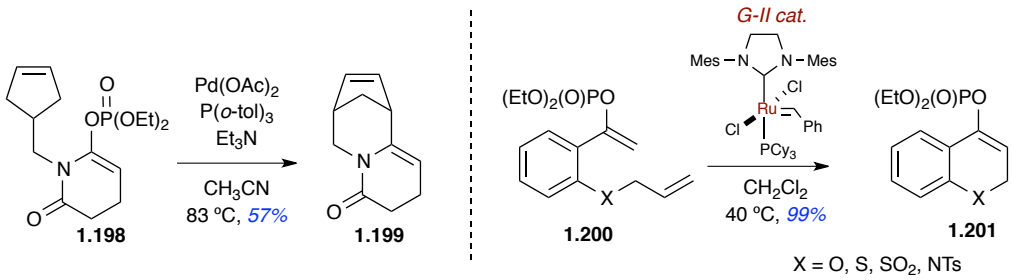


In 2000, Coe and coworkers developed an intramolecular Heck cyclization on enol phosphate **1.198** to construct the tricyclic skeleton of compound **1.199** in their

total synthesis of (±)-cytisine (Scheme 33).[91] While both enol triflate and phosphate underwent the cyclization, the phosphate-activated intermediates were found to be more robust.

In 2003, Hanson and coworkers demonstrated the first RCM of an enolphosphate using the Grubbs second-generation catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$] and showed facile generation of a variety of cyclic enol phosphates **1.201**(Scheme 33).[92]

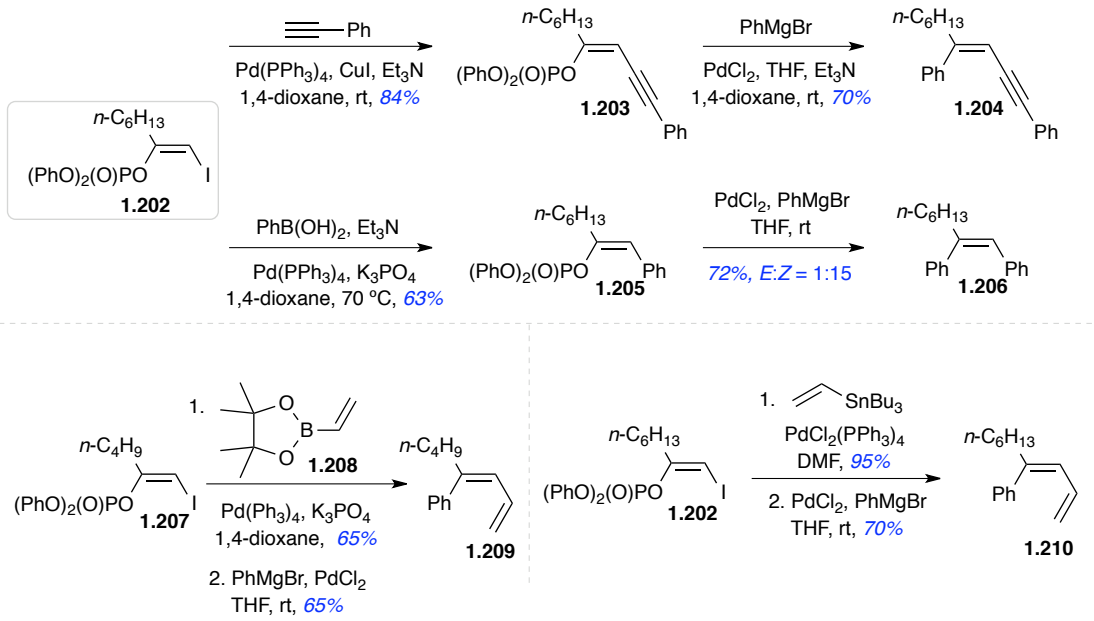
Scheme 33



In 2011, Kim, Lee and coworkers demonstrated an impressive regio- and stereoselective synthesis of trisubstituted alkenes via different Pd-catalyzed consecutive cross-coupling reaction sequences (Scheme 34). Bisfunctional (*Z*)-alkenyl iodophosphates **1.202**, prepared via a previously reported Au-catalyzed reaction, were coupled in a Sonogashira/Kumada reaction sequence with ethynylbenzene and PhMgBr, through intermediate **1.203**, to yield (*Z*)-3-en-1-yne product **1.204**. Similarly, product **1.206** was synthesized through a Suzuki/Kumada reaction sequence involving intermediate **1.205**. In an alternative Suzuki/Kumada sequence, **1.207** was treated with vinylboronic acid pinacol ester **1.208**, followed by

coupling with PhMgBr, to afford (*Z*)-1,3-diene **1.209**. Moreover, the authors also utilized a Stille/Kumada sequence to afford the (*Z*)-1,3-diene **1.210** from (*Z*)-alkenyl iodophosphates **1.202** (Scheme 34).

Scheme 34

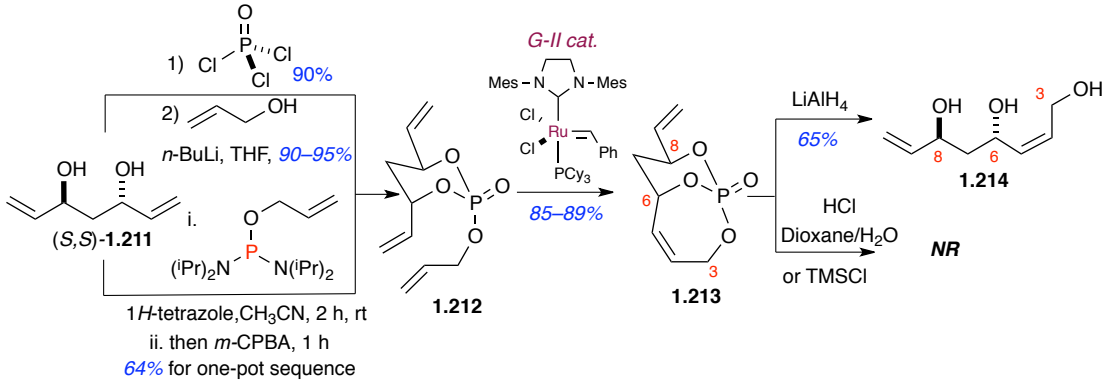


1.3.4. Phosphate tethers

Hanson and coworkers demonstrated the utility of phosphates as temporary tethers capable of uniting advanced intermediates using di-and tripodal coupling characteristics of phosphates. In addition, orthogonal protection and innate leaving group properties of phosphate tethers was demonstrated.[93] In 2005, Hanson and coworkers reported a phosphate-tether-mediated desymmetrization of the C_2-symmetric 1,3-*anti*-diol diene **1.211** to generate the unique bicyclo[4.3.1]phosphate (*S,S,S*$_P$)-**1.213** using [(IMesH$_2$)(PCy$_3$)(Cl)$_2$Ru=CHPh; *G-II cat*] (Scheme 35).[94] In 2013, Hanson and coworkers reported a number of more elaborate examples of

phosphate-tether-mediated desymmetrizations [95] It should be noted that this temporary tether could be removed by treatment with $LiAlH_4$ to afford triol **1.214** as a single diastereomer.

Scheme 35



The inherent properties of phosphate, as well as the overall stability of its [4.3.1]-bicyclic variant (particularly stability to acid promoted hydrolysis), have led to the development of a number of synthetically useful transformations of the bicyclo[4.3.1]phosphate (S,S,S_P)-**1.213**, [or its diastereomeric (R,R,R_P)-counterpart] (Scheme 36). In particular, a chemo-selective hydrogenation of the exocyclic olefin (**1.215**), a diastereoselective cuprate addition (**1.216** and **1.217**), and successful cross-metathesis of type I and type II olefins with the exocyclic double bond (as in example **1.220**), along with a variety of other transformations, have allowed for the generation of other mono- and bicyclic phosphates.[58c, 96] Most notably, the coupling of orthogonal transformations in a multi-step, one-pot, sequential RCM/CM/H_2 process.[58c,97] has allowed for the facile generation of advanced intermediates en route to the total synthesis of natural products (Figure 9).[98]

Scheme 36

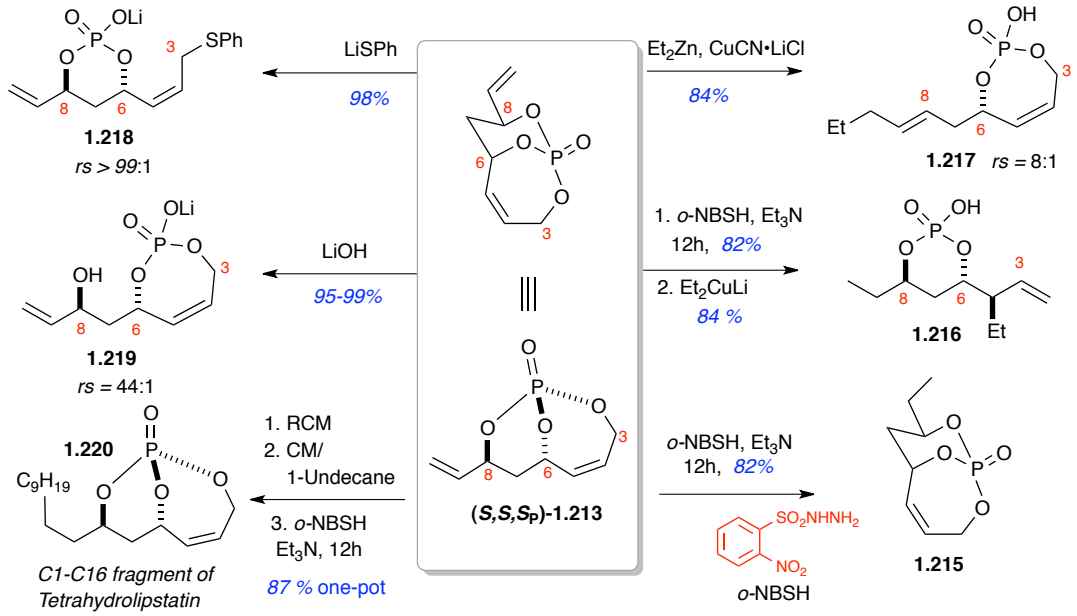
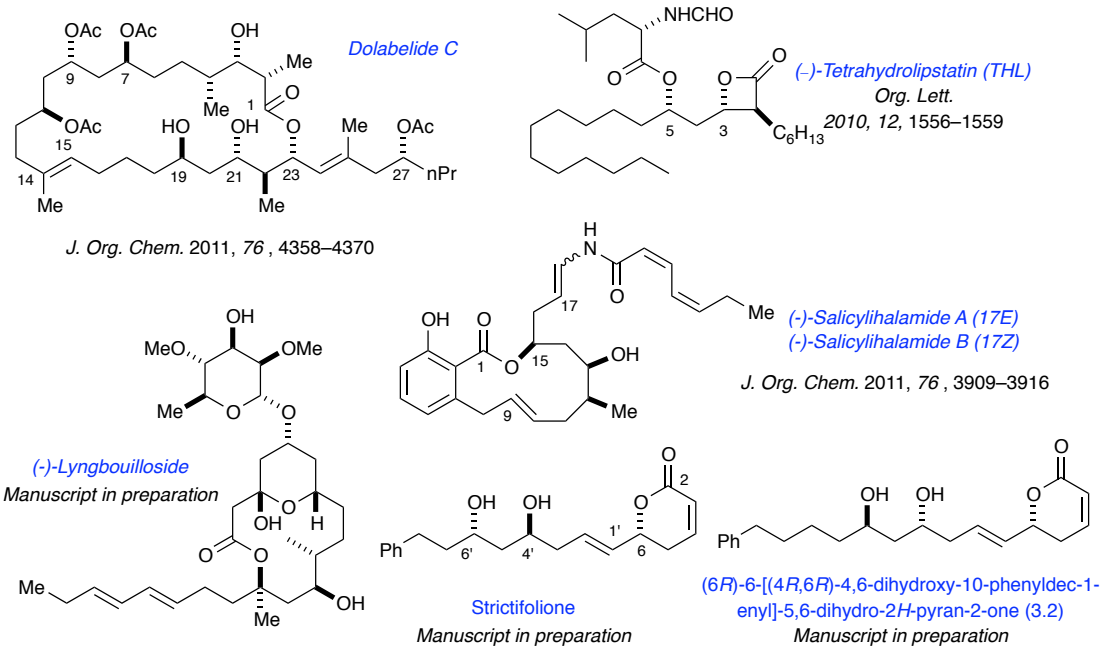


Figure 9: *Natural products synthesized utilizing phosphate tether methodology.*



1.4 Conclusion

The importance of phosphates in biology as well as in organic synthesis has been highlighted. Prominent biological activities inherent to phosphate-containing natural products, as well as medicinally important active drugs and associate prodrug strategies, have also been discussed. While the use of phosphates in synthesis has historically been overshadowed by their ubiquity in nature—where key enzyme-catalyzed processes dominate several biological pathways—a number of new synthetic methods are beginning to counter this historical viewpoint. This trend will undoubtedly continue to emerge as new studies aimed at shedding light on the unique chemistry and biology of phosphates, carry on.

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Chapter 2

Synthetic studies towards fostriecin and 8-epimer

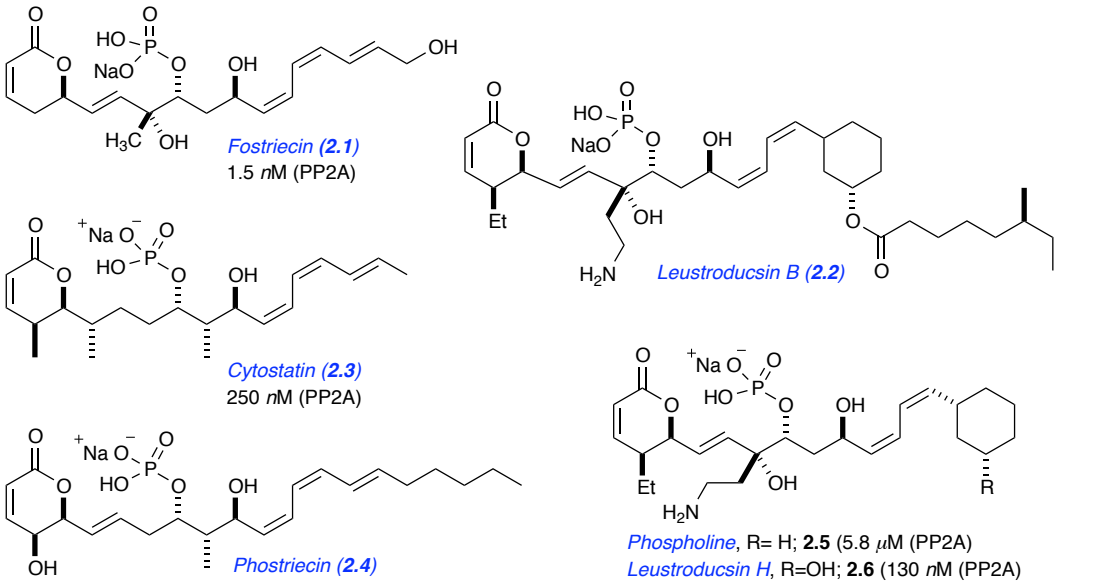
2.1 Introduction

2.1.1 Overview of fostriecin

Fostriecin (**2.1**, CI-920, Figure 1) is a structurally unique phosphate monoester isolated from *Streptomyces pulveraceus* by workers at Warner Lambert-Parke Davis in 1983,[1] and is a potent PP2A inhibitor (IC_{50} 1.5 *n*M) as well as a weak inhibitor of type I serine/threonine protein phosphatase (PP1; IC_{50} 131μM).[2] It exhibits *in vitro* antitumor activity against a broad range of cancerous cell lines including lung cancer, breast cancer, and ovarian cancer, and displays *in vivo* inhibitory activity against mouse leukemia cell lines (L1210, IC_{50} 0.46 μM and P338).[3] Based on early studies, its antitumor activity was suggested to be due to the inhibition of topoisomerase II.[4] However, recently it has been shown to operate via an inhibitory pathway of the mitotic entry checkpoint through a more potent inhibition of protein phosphatase 2A (PP2A), selectively over the PP1 (selectivity: PP2A/PP1>10^4–10^5).[2,5] Despite this promising activity, NCI-supported clinical trials were suspended due to the drug instability and unpredictable purity of the natural product.

In 1997, Boger and coworkers determined the relative and absolute stereochemistry in fostriecin that confirmed previous assignments in a family of biologically active and structurally related natural products, including leustroducsin B (LSN-B, **2.2**), cytostain (**2.3**) and phoslactomycin C (**2.7**).[6,7] In 2013, Tang and coworkers reported a comprehensive post-PKS (polyketide synthase) modification mechanism for fostriecin biosynthesis via elucidation of the fostriecin biosynthetic gene cluster.[8]

Figure 1: *Fostriecin family of phosphate-containing natural products.*



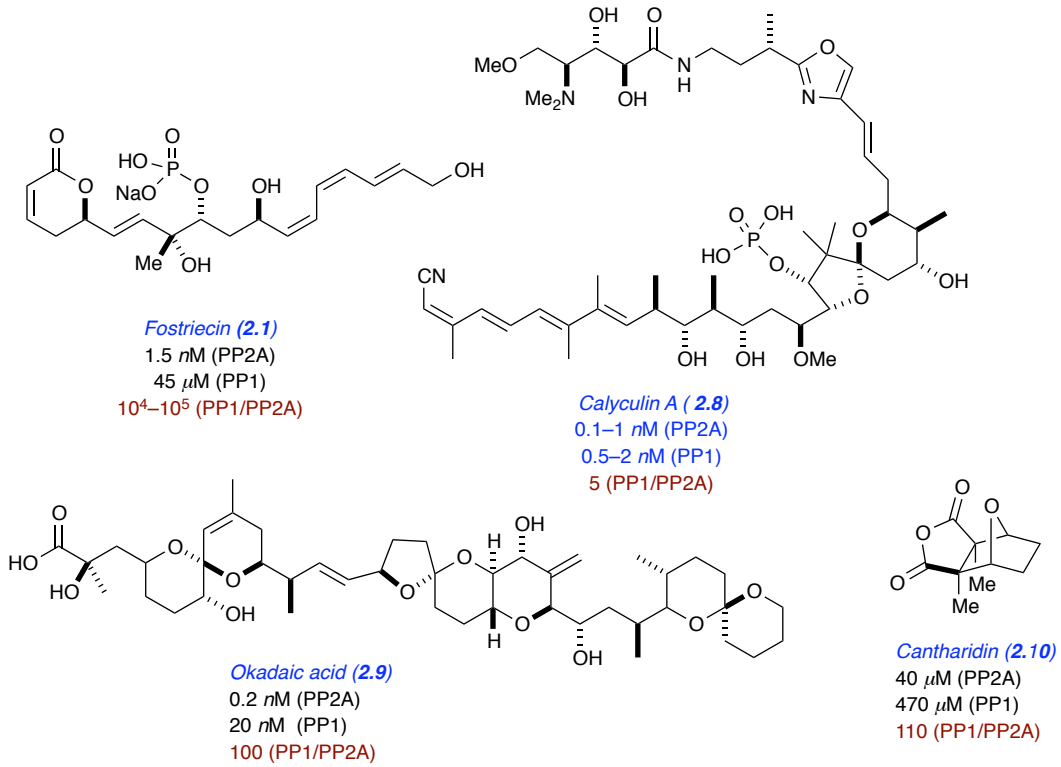
2.1.2 Structure-Activity Relationship (SAR) studies of 2.1 and analogs

As mentioned previously, fostriecin is the most selective protein phosphatase (PP2A) inhibitor (IC_{50} 1.5 *n*M) studied to date among the well-known naturally occurring PP2A selective inhibitors such as okadaic acid (IC_{50} 0.2 *n*M), cantharidin (IC_{50} 40 μM) and the calyculin family (IC_{50} 0.1–1.0 *n*M, Figure 2).[9] The selectivity of fostriecin is on the order of 10^4–10^5 times more selective for PP2A and its homolog PP4, than PP1. In contrast, the selectivity for PP2A/PP4 over PP1 is only 100 times for okadaic acid, 10 fold for cantharidin and 5 fold for calyculin (Figure 2).[9]

Fostriecin also has many of the elements of the common pharmacophore that was proposed for the natural inhibitors such as the calyculins, okadaic acid and cantharidin. These inhibitory structural features include (i) the acidic group

[carboxylate (masked) or phosphate] that is proposed to interact with key metal ions residing within a phosphatase, (ii) the methyl substituent proximal to the acidic moiety, that are proposed to mimic the methyl group in phosphothreonine, and (iii) the hydrophobic segment that is assumed to mimic the hydrophobic amino acid residues adjacent to phosphothreonine.[9] However, the most significant feature that sets apart the fostriecin family from other previous PP2A inhibitors is the unsaturated lactone. The Michael-accepting capabilities of this moiety, *vide infra*, have driven speculation from the beginning that it is responsible for the observed selectivity in fostriecin.

Figure 2: *Natural PP2A inhibitors.*



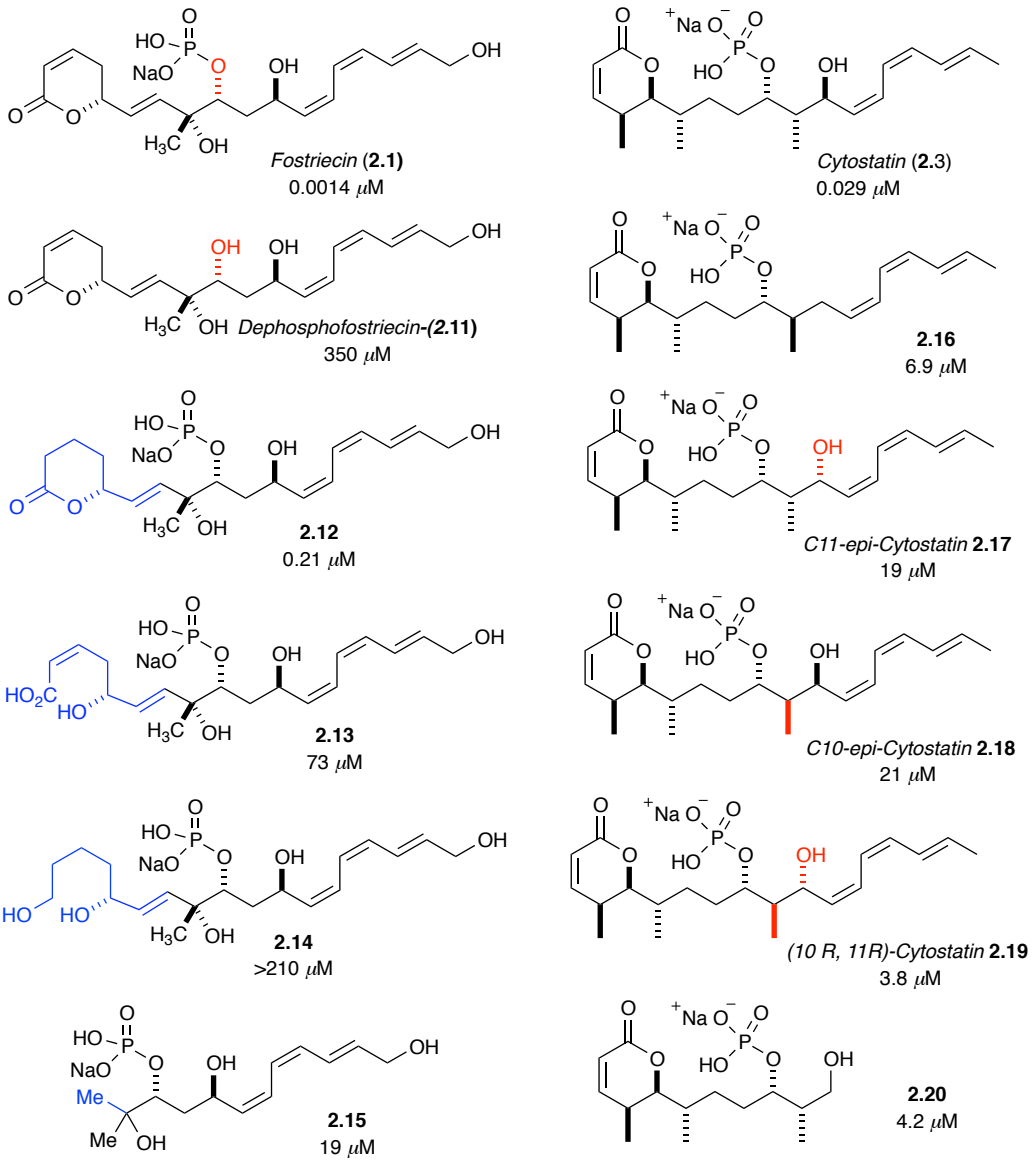
In 2003, Boger and coworkers reported seminal SAR studies related to

fostriecin, which addressed the relevance of the α,β-unsaturated lactone and the free phosphate moiety in selective PP2A activity.[10] In 2009, Boger, Honkanen and others reported SAR studies for fostriecin and the structurally related natural serine/threonine phosphatase inhibitor cytostatin, and their respective analogs, against PP1, PP2A, and PP5.[11] According to these studies, it was found that the phosphate moiety is critical for PP2A inhibition as demonstrated by a 10^5-fold loss of activity for both dephosphofostriecin **2.11** and dephosphocytostatin (Figure 3). Furthermore, C8–C9 phosphodiester analogs of **2.1** displayed 10^3-fold loss in activity, while an acetate-protected C11 analog demonstrated a further 50-fold loss in activity, indicating the importance of the C11-hydroxy group to fostriecin potency.[11] Moreover, the hydrolyzed lactone also experienced a 10^5-fold loss in activity. However, compound **2.15**, void of a lactone, also shows significant, but diminished PP2A inhibitory activity (200-fold loss in activity). Fostriecin analogs with variation in the eastern triene moiety were also studied. In particular, analog **2.20** (Figure 3) lacking the entire (*Z,Z,E*)-triene, also strongly inhibits PP2A, while having little effect on PP1 or PP5. Therefore, it was suggested that both lactone and the triene contribute to the overall selectivity.

Despite the aforementioned studies, comprehensive stereochemical SAR studies—highlighting the effects of the four-stereogenic centers in fostriecin—are lacking in the literature. Studies performed on cytostatin diastereomers **2.17**, **2.18**, and **2.19** showed that they are less potent inhibitors of PP2A compared to the natural compound.[12] Shibasaki and Kanai reported that the inhibitory activity for PP2A and

PP1 is slightly weaker 8-*epi*-fostriecin, but more selective for PP2A inhibition compared to natural fostriecin.[13]

Figure 3: *IC 50 values for PP2A inhibition of fostriecin and its analogs.*

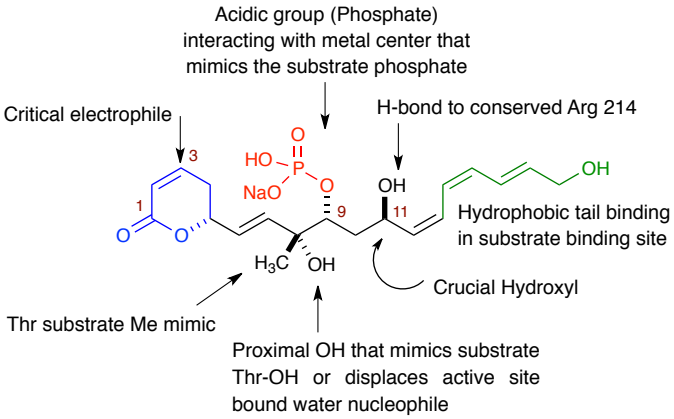


Docking studies with fostriecin also shed additional light demonstrating several key interactions whereby fostriecin was found to be bound with the phosphate

moiety coordinated to active-site metals and forming H-bonds with active site residues.[10,11] In addition, the triene was found to reside in the acidic groove, and the lactone is located in a pocket formed by Arg^{89} and four residues in the β12-β13 loop (Tyr^{265}, Cys^{266}, Arg^{268}, Cys^{269}) suggesting that it was prepositioned for nucleophilic attack at the γ-position of the lactone. Interestingly, it should be noted that the Cys^{269} residue containing a thiolate nucleophile is unique to PP2A and PP4 and absent in PP1, PP2B, PP5 and PP7, thereby potentially explaining the highest selectivity for PP2A over PP1 ($> 10^4$–10^5) and PP5 ($> 10^4$–10^5). Hence, it is now assumed that the 200-fold increased potency in fostriecin is due to Cys^{269} alkylation within the active site loop, which also explains the higher selectivity observed for the fostriecin family for PP2A inhibition in comparison to the other natural PP2A inhibitors (calyculin, okaidic acid, etc.) that do not possess a lactone subunit.[11]

In 2009, Sugawara and coworkers reported an *in vitro* study and showed that fostriecin covalently binds to the Cys^{269} residue of PP2A in Hela S3 cells.[14] In this study, they employed pull-down assays using synthetically prepared, biotin-labeled, fostriecin (bio-fos) in conjunction with, matrix-assisted laser desorption/ionization time-of-flight mass spectrometric analysis. Additionally, binding models constructed for PP2A-conjugated fostriecin (via binding of the lactone with the Cys^{269} residue), demonstrated that the C9 phosphate binds or interacts with manganese cations within the active site of PP2A. Overall, this results in conjugation of fostriecin to PP2A, and thus prevents natural substrate from entering the active site, which also further explains the decreased activity for dephosphorylated fostriecin (**2.11**, Figure 3).

Figure 4: *Important structural features associated with PP2A inhibition.*



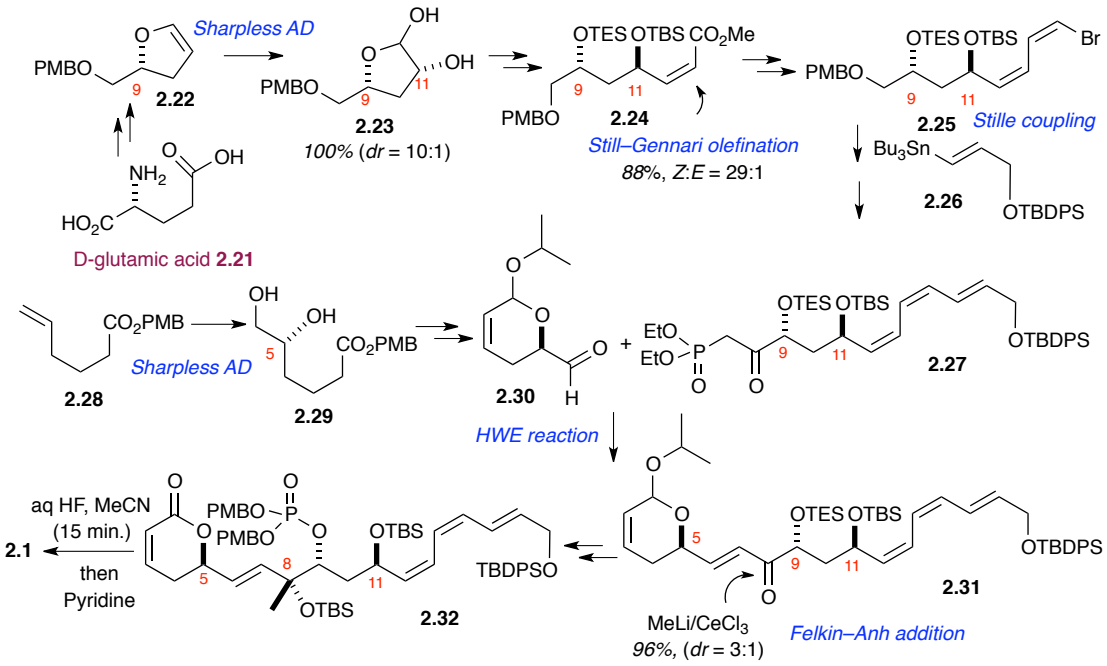
2.1.3 Synthetic studies of fostriecin:

Boger and coworkers determined the 3-D structure of **1** through synthetic and degradation studies.[15] Since this seminal work, several total syntheses[16] and synthetic studies[17] have been reported. Key synthetic strategies utilized in these total syntheses are highlighted below.

In the 2001 seminal synthesis of **2.1** by Boger and coworkers, the C5 and C11 stereocenters were established employing Sharpless asymmetric dihydroxylation of dihydrofuran **2.22**, while the C9 center was generated from D-glutamic acid (**2.21**, Scheme 1). The C8 tertiary center was installed using MeLi/$CeCl_3$ addition into the C8 carbonyl of **2.31**, and operated under Felkin-Ahn control. The sensitive *Z*,*Z*,*E*-triene subunit was introduced in a step-wise manner utilizing Still-Gennari conditions to install the C12–C13 *Z* olefin in **2.24**, as well as Wittig olefination for generation of the C14–C15 *Z* olefin. Subsequent Stille coupling of **2.25** and **2.26** enabled installation of the C16–C17 *E* olefin containing fragment. The lactone subunit **2.30**

was introduced at a late-stage of the synthesis using Wadsworth–Horner–Emmons (HWE) coupling of ketophosphonate **2.27** and aldehyde **2.30**, while also constructing the C7–C8 *E*-configured olefin. The phosphate group at C9 was introduced as a *bis*-PMB-protected ester and final deprotection was achieved through a two-stage protocol using HF (5% H_2O–CH_3CN, 15 min) to remove the PMB esters, followed by addition of pyridine (25 % pyr–CH_3CN/H_2O) for slow exhaustive deprotection of all silyl ethers.

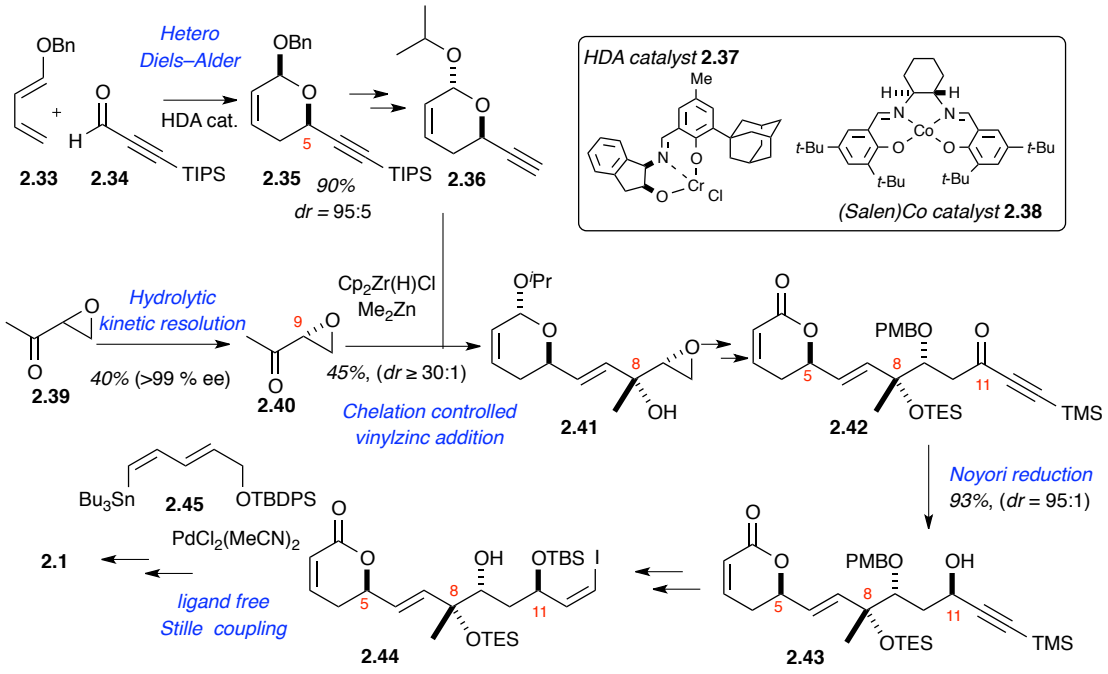
Scheme 1



In 2001, Jacobsen completed the total synthesis of fostriecin in a route comprised of a longest linear sequence (LLS) of 19 steps,[16a] highlighting the use of a Cr-mediated catalyst in a hetero-Diels-Alder (HDA) reaction to obtain alkyne lactol **2.36**. Subsequent zirconium-mediated addition to chiral epoxy ketone **2.40**—which was

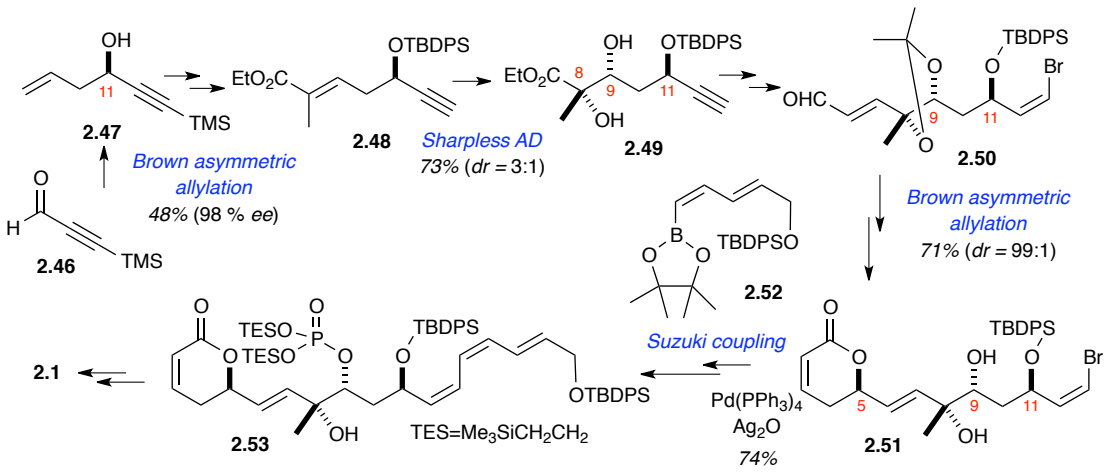
obtained via the [(salen)Co] catalyst **2.38**—catalyzed the hydrolytic kinetic resolution of the racemic epoxy ketone **2.39**, which established three of the four stereogenic centers at C5, C8 and C9.[16a] The carbinol stereochemistry at C11 was installed by Noyori reduction of propargyl ketone **2.42** and the C12–C13-*Z*-configured olefin was produced by *cis* reduction of the alkyne using diimide conditions. The "ligand free" Stille coupling of vinyl iodide **2.44** and vinyl stannane **2.45** was next employed to construct the remaining C14/C15-*Z* and C16/C17-*E* configured olefin geometries in **2.1**. Phosphate installation and deprotection were achieved using the previously reported conditions of Boger.

Scheme 2



In 2002, Falck and coworkers reported the total synthesis of **2.1** with an LLS of 22 steps.[16b] The secondary hydroxy stereocenters at C11 and C5 were installed employing Brown asymmetric allylation of aldehyde **2.46** and **2.50**, respectively. The Sharpless asymmetric dihydroxylation with AD-mix β of the trisubstituted olefin at C8–C9 in **2.48** established both stereocenters at C8 and C9 in a single step. Diimide *cis* reduction of the alkyne generated the requisite C12–C13-*Z* olefin geometry. The triene moiety was constructed utilizing Suzuki–Miyaura cross coupling between vinyl bromide **2.51** and vinyl boronate **2.52** and the phosphate function at C9 was introduced as a *bis*-(2-trimethylsilylethyl) phosphate triester, while global desilylation was achieved by treatment with HF•pyridine at room temperature.

Scheme 3

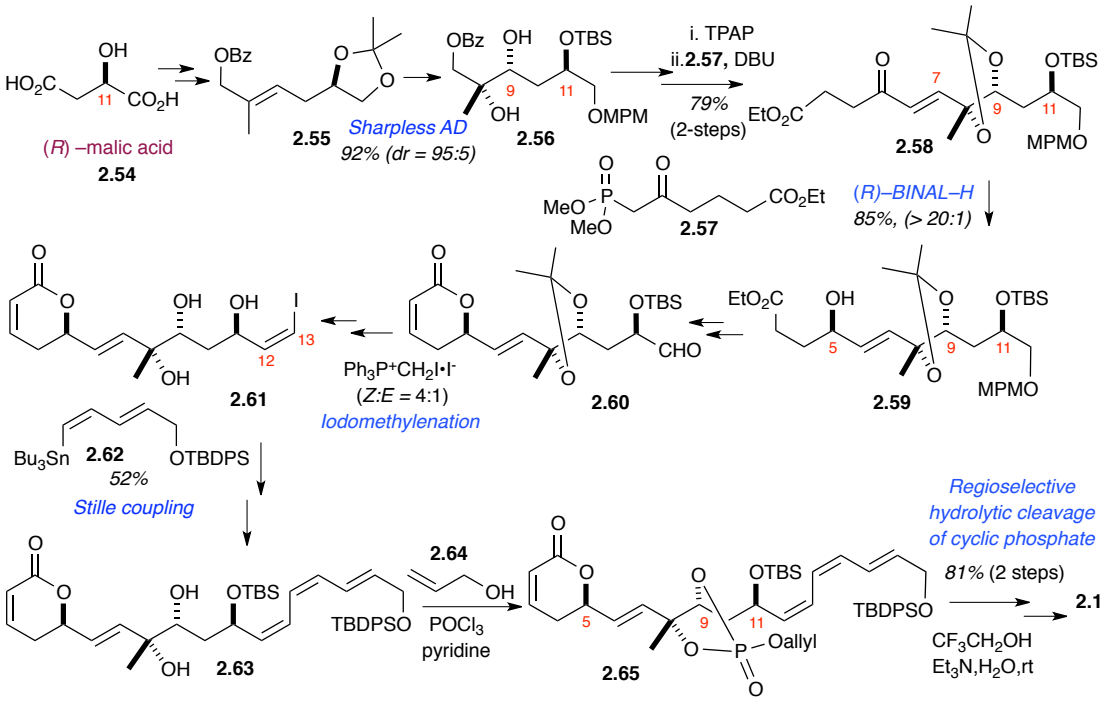


In 2002, Imanishi and coworkers accomplished the total synthesis in 24 linear steps via a highly convergent route involving a 3-segment coupling procedure and the aforementioned highly innovative method for phosphate installation, *vide supra*

(Chapter 1).[16c] (*R*)–Malic acid served as the source for the C11 carbinol center, while the C8 and C9 stereocenters were introduced using Sharpless asymmetric dihydroxylation of the trisubstituted allylic alcohol moiety in **2.55**. The unsaturated lactone subunit was constructed applying HWE reagent **2.57**, while stereoselective reduction of the resulting ketone **2.58** with (*R*)–BINAL–H established the required C5 stereocenter with excellent selectivity (*dr* = 20:1). It should be noted that since attempts on direct substitution of the *Z*, *Z*, *E*, triene under Wittig conditions were not successful, a 2-step protocol was employed installing the C12–13-*Z* olefin via iodomethylation, followed by Stille coupling with *Z,E*-configured stannane **2.62**.

In the final stages of the Imanishi fostriecin synthesis, introduction of the C9 phosphate group was achieved by formation of a cyclic phosphate triester, followed by regioselective hydrolytic cleavage using CF_3CH_2OH:H_2O:Et_3N (20:1:1) to afford good selectivity (~7:1). This selectivity was assumed to be governed by a combination of stereoelectronic (in the 5-membered cyclic phosphate, the endo–cyclic P–O bond is cleaved more easier than the exo-cyclic P–O bond) and steric effects (sterically more hindered P–O bond is cleaved easily).

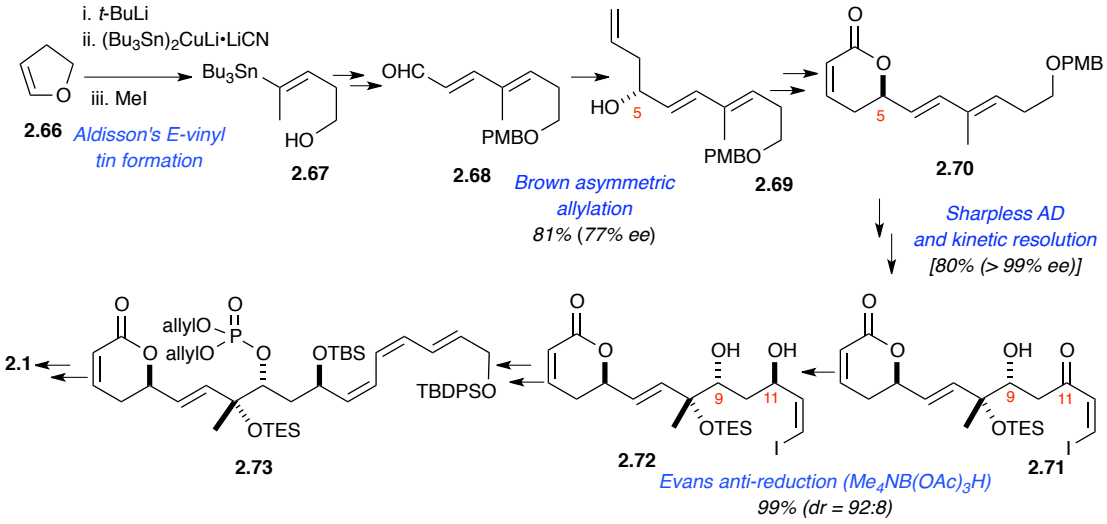
Scheme 4



In 2002, Hatakeyama and coworkers[16d] reported the synthesis of **2.1** from dihydrofuran in 21 steps using the following key reactions: (i) Brown allylation of aldehyde **2.68** to establish the C5 stereocenter, (ii) Sharpless dihydroxylation of **2.70** to install the hydroxyl centers at C8 and C9 and (iii) Evans *anti*-selective reduction of ketone **2.71** with $Me_4NBH(OAc)_3$ to introduce the C11 hydroxy stereochemistry (Scheme 5). The *Z,Z,E* triene fragment was installed following a similar protocol used in the Jacobsen synthesis, whereby *Z*-selective iodination using the Stork protocol was followed by Stille coupling. In this synthesis, an allyl group was employed to protect the phosphate in order to circumvent problems associated with final global deprotection in previous syntheses (i.e. long reaction times and moderate

yields). Mild deprotection of the allyl group was successfully achieved under Pd-catalysis [$Pd(PPh_3)_4$, $HCONH_2$].

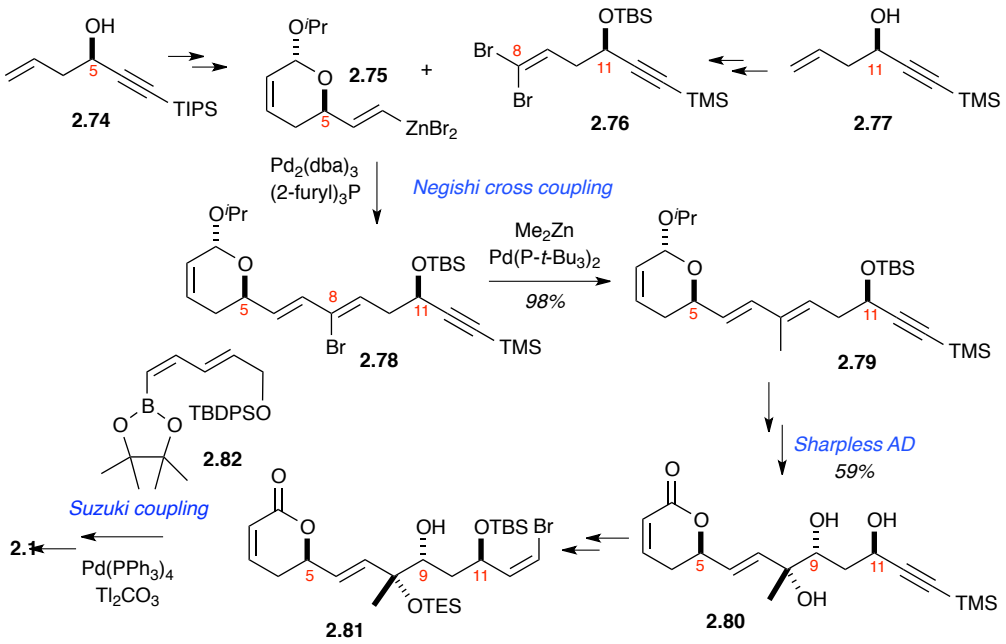
Scheme 5



In 2009, McDonald and coworkers[16e] reported a highly convergent synthesis of fostriecin in 16 linear steps (Scheme 6). The key reactions in their synthesis, included: (i) a Pd-catalyzed Negishi coupling of vinyl zincate **2.75** and dibromide **2.76** to form the C7–C8 bond, followed by second cross-coupling of the resulting bromo compound **2.78** and dimethyl zinc to install the C8 methyl substituent, and (ii) late-stage regioselective Sharpless dihydroxylation of the C8–C9 central diene utilizing the less sterically demanding monomeric ligand DHQD-4-MEQ to generate the requisite hydroxyl centers at C8 and C9. Incorporation of the C14–C17 *Z*,*E* diene into the C12/C13-*Z*-configured bromoalkene was achieved through Suzuki-Miyaura

cross coupling of **2.81** and **2.82** in the presence of thallium carbonate (Tl_2CO_3) at room temperature to afford a higher yield as well as shorter reaction time.

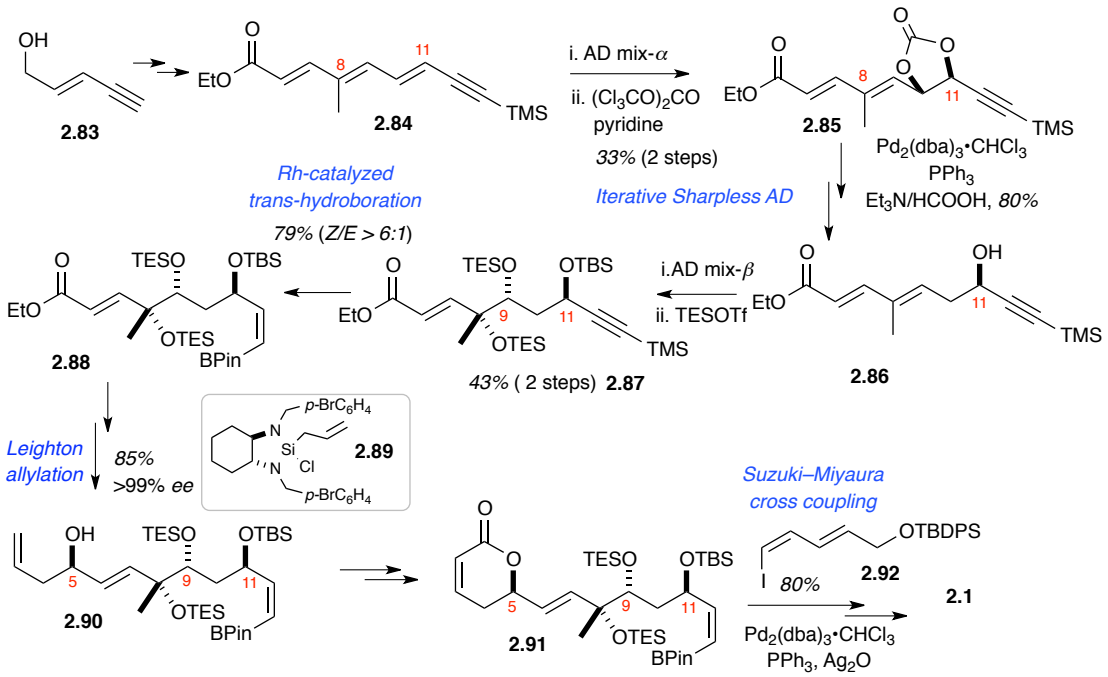
Scheme 6



In 2010, O'Doherty and coworkers reported another total synthesis for **2.1** that entailed an LLS of 26 steps highlighting the utility of an iterative Sharpless AD reaction to establish the C11, C9 and C8 stereogenic centers (Scheme 7).[16g] Asymmetric dihydroxylation of the most electron-deficient double bond of trienoate **2.84** with AD mix-α and subsequent Pd-catalyzed reduction was used to install the C11 hydroxyl center. A second Sharpless asymmetric dihydroxylation (SAD) of dienoate **2.86** with AD mix-β generated the C8 and C9 hydroxyl centers, while Leighton asymmetric allylation of the aldehyde derived from **2.88** generated the C5 stereocenter. Introduction of C12–C18 triene fragment was achieved via the

synthesis of vinyl boronate **2.88** by Rh-catalyzed *trans*-hydroboration and Suzuki-Miyaura cross-coupling with vinyl iodide **2.92**. An additional innovative feature of the O'Doherty route was the remarkable stability of the vinyl pinacol boronate **2.88** that was stable to silica gel chromatographic separations, as well as several subsequent chemical transformations, including: DIBAL reduction, MnO_2 oxidation, Leighton allylations, and $Cl_2(PCy_3)_2Ru$=CHPh-catalyzed ring-closing metathesis (RCM).

Scheme 7



In addition to the aforementioned total syntheses, several formal total syntheses to **2.1** were also reported.[17] In 2005, Trost completed dephospho-fostriecin in 14 linear steps employing a direct asymmetric Zn-catalyzed aldol reaction.[18] In 2002, Shibasaki's formal synthesis utilized four asymmetric catalysts to set the four

central stereogenic centers, including cyanosilylation of a ketone to install the C8 tertiary alcohol, Yamamoto allylation to set C5, use of a Bronsted base, two-centered asymmetric catalyst LLB (L=La, L=Li, B=BINOL)[19] to control the aldol reaction and set the C9 carbinol, as well as employment of Noyori hydrogenation for generation of the C11 carbinol.[20,21]

2.2 Results and discussion

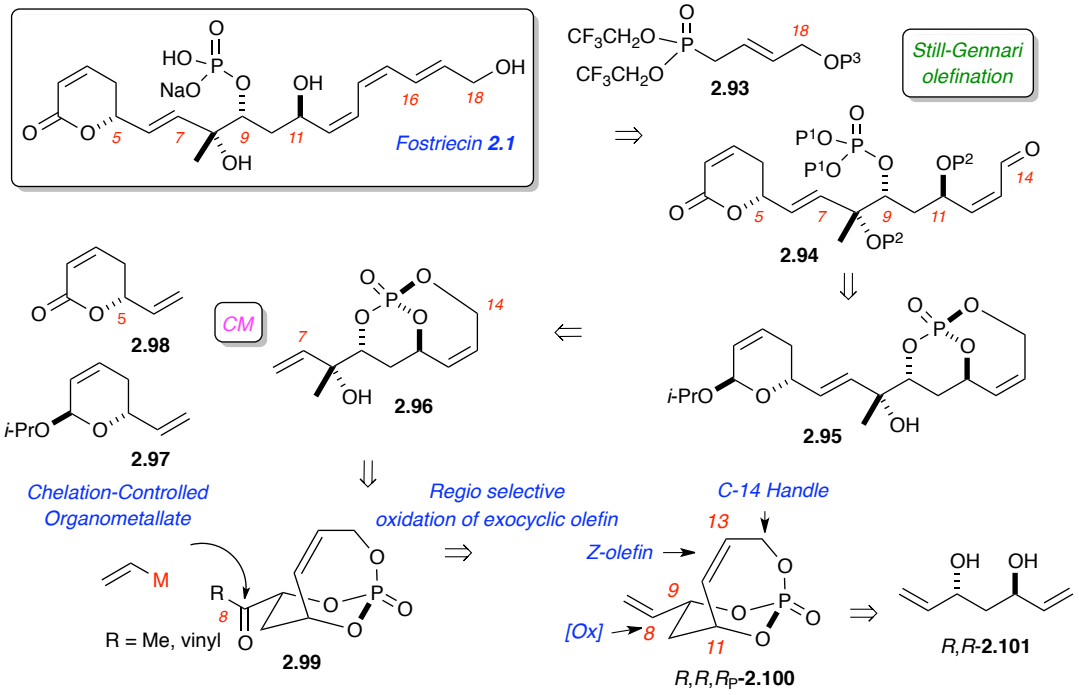
Despite the breadth of synthetic efforts reported toward fostriecin, library-amenable synthetic routes are still challenging and in high demand due to its overall potency and selectivity. Moreover, currently there is a lack of SAR studies assessing the effects of the four stereogenic centers within **2.1**, as well as the potential effect of lactone surrogates. In considering a synthetic route for fostriecin, attention in our work was particularly focused on designing a route that not only accessed fostriecin, but would also enable generation of useful analogues as probes. For this purpose, we disclose a phosphate-tether mediated, modular approach en route towards fostriecin and its C8 epimer. In addition, effort toward developing a viable synthetic route for installation of lactone surrogates, are also reported.

2.2.1 Retrosynthetic analysis

In considering the architecture of fostriecin, a route was envisioned entailing the use of **2.95** as a key intermediate bearing all four requisite stereogenic centers and olefin geometries (Scheme 8). The anticipated synthetic pathway centered on cross-metathesis (CM) between the isopropyl-lactol **2.97** or lactone **2.98** with

phosphate **2.96** that would eventually provide flexibility in potential analog generation. Phosphate **2.96** can be synthesized from organometallic addition to the ketone **2.99** and depending on the organometallic reagent, the selectivity for the C8 center or the C8 epimer can be altered. The entire sequence starts from the previously reported bicyclic phosphate (R,R,R_P)-**2.100**.[22] Installation of the key C8–C14 subunit employs a simple terminus differentiation strategy of the C_2-symmetric *anti*-diol (*R*,*R*)-**2.101** using a phosphate tether/RCM strategy to derive (R,R,R_P)-**2.100**. Notably, in addition to desymmetrization of the central 1,3-*anti*-diol subunit, this phosphate tether-mediated process serves to further establish in a single step the requisite C12/C13 *Z*-configured olefin, the C7 terminal olefin armed for regioselective oxidation, and triol protection at the C9, C11, and C14 carbinol centers.

Scheme 8: *Retrosynthetic analysis*

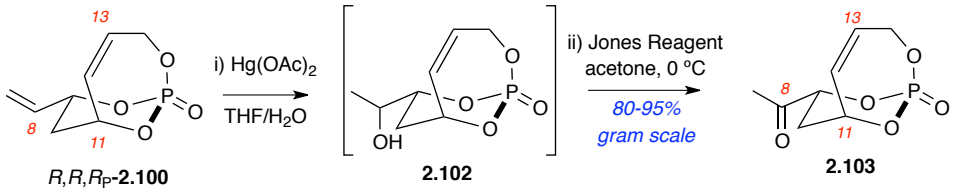


2.2.2 Synthetics studies to 2.1

Synthetic studies began with a regioselective oxidation of (R,R,R_P)-**2.100** (Scheme 9). The enantiomeric pair of bicyclic phosphates, (R,R,R_P)-**2.100** and (S,S,S_P)-**2.100**,[23] have been previously utilized in the total synthesis of dolabelide C, tetrahydrolipstatin and salicylihalamide and gram-scale syntheses of either enantiomer of **2.100** can now be routinely carried out. Initially, it was discovered that reactions using standard Wacker conditions,[24] resulted in complete recovery of starting material in 80–90% yield. However, this outcome was not unexpected since protected allylic alcohols are known to be problematic, if not completely unreactive, towards Wacker oxidation.[25] Upon rigorous investigation, it was found that employing modified-Wacker conditions[26,27,28] provided initial yields of 40% of desired ketone. Optimization of this protocol utilizing (R,R,R_P)-**2.100**, yielded (R,R,R_P)-**2.103** in 65% yield on gram-scale.

Additional optimized conditions were next developed where oxy-mercuration, was employed followed by addition of $CuCl_2$ to yield alcohol **2.102**, after which the solvent was removed and the crude alcohol was directly subjected to Jones oxidation to provide (R,R,R_P)-**2.103** in gram-scale affording yields of 80–95% (Scheme 9). Purification involved simple passage of the crude mixture through a silica plug to remove any associated metal ions. This protocol also highlights the exquisite acid stability of the bicyclic phosphate system while being more robust than the Pd-mediated route.

Scheme 9



*R,R,R*P-**2.100** **2.102** **2.103**

Investigations next focused on developing a diastereoselective addition of vinyl magnesium bromide into methyl ketone (*R*,*R*,*R*P)-**2.103** to generate phosphate **2.104**, the key intermediate in both total and analog syntheses. Based on model studies, and literature precedent,[29] it was postulated that the less hindered *Re* face attack (see **2.105** in Scheme 10) of the vinyl Grignard addition under chelation control would generate the requisite C8 stereocenter in fostriecin. First, vinyl magnesium addition was examined and addition of 3 equivalents of freshly prepared vinyl Grignard to (*R*,*R*,*R*P)-**2.103** at -78 ºC in THF for 7 hours provided vinyl phosphate **2.104** in 43 % isolated yield (77 % BRSM) and 15:1 diastereomeric ratio (It should be noted that use of commercially available vinyl magnesium bromide gave inferior results as compared to freshly prepared Grignard). Increasing the temperature or addition of more equivalents of vinyl Grignard reagent, did not improve the yield, but led instead to the attack at phosphorus. Interestingly, Lewis acid activation of the ketone with addition of 1.0 equivalent of BF_3•Et_2O was able to complete the reaction within 1–1.5 hours even at a temperature of -82 ºC (73% yield) and with excellent diastereoselectivity (12:1). With this promising result in hand, the stereochemical outcome of the reaction was further examined with X-ray

crystallography (Scheme 10). Surprisingly, it was found that the major isomer was the C8 (8*S*)-**2.104** (8-*epi*-**2.104**), not the requisite C8 center (8*R*)-**2.104**, as expected. Hence, efforts were focused on understanding the outcome of the Grignard addition reaction into the bicyclic ketone **2.103**.

Scheme 10: *Diastereoselective Grignard addition*

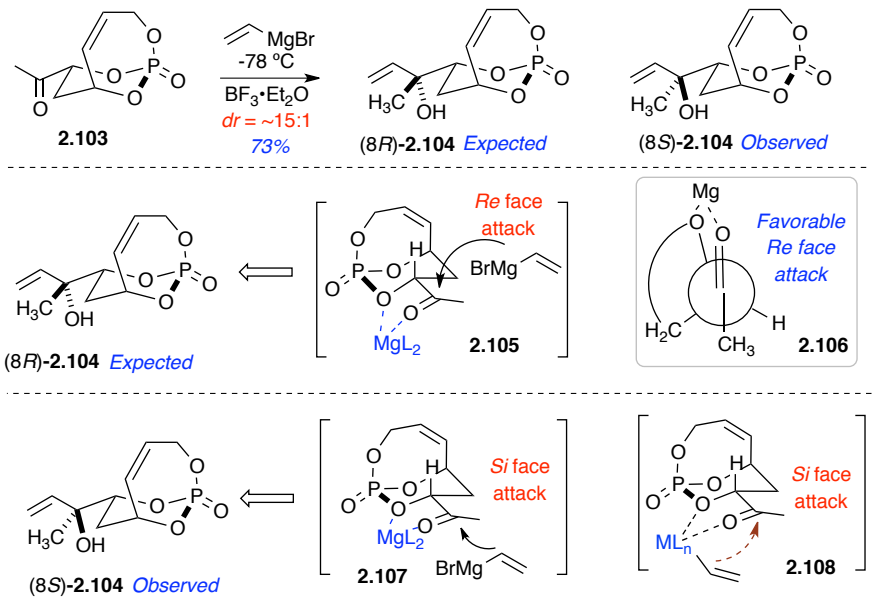


Figure 5: *X-Ray structure of (8S)-**2.104** (8-epi-**2.104**).*

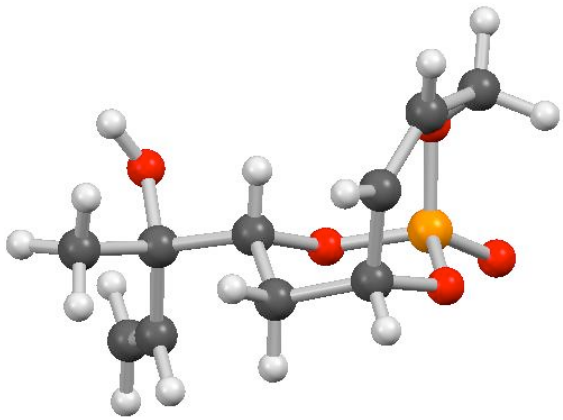


Table 1

entry	*Conditions*	*dr*	*entry*	*Conditions*	*dr*
1	BF_3•Et_2O	13:1	7	$CeCl_3$•LiCl	6:1
2	BF_3•Et_2O, -0 ºC	9:1	8	$ZnCl_2$/ $ZnBr_2$ Vinyl MgBr	Not obs.
3	$TiCl_4$	18:1	9	**HMPA**	**4:1**
4	CuI	Not obs.	10	**DMPU**	**5:1**
5	$ScCl_3$	18:1	11	MAD	Not obs.
6	**$YbCl_3$-Vinyl MgBr**	**50:1**	12	**$CeCl_3$•LiCl-Vinyl MgBr**	**2 : 1**

We anticipated that applying chelating reagents[30] superior to than Mg would provide enhanced hindrance at the *Si* face (see **2.107**) of the ketone and thereby facilitate *Re*-face attack to form the chelation-controlled product (8*R*)-**2.104 (**Scheme 10). Several vinyl metallic reagents were added to ketone **2.104** at -78 ºC to investigate this hypothesis (Table 1). Diminishing our expectations empirical results further proved that better chelating reagents drastically increased the selectivity for the C8 epimer 8-*epi*-**2.104** [(8*S*)-**2.104**]. Vinyl Grignard addition, in the presence of $TiCl_4$,[31] produced the C8-epimer with enhanced selectivity (18:1) (Table 1, entry 3), whereas use of $CeCl_3$•LiCl,[32] gave reduced selectivity (6:1) (Table 1, entry 7). In all the aforementioned cases, metal reagents were added as Lewis acids without pre-incubation with the organometallic reagent.

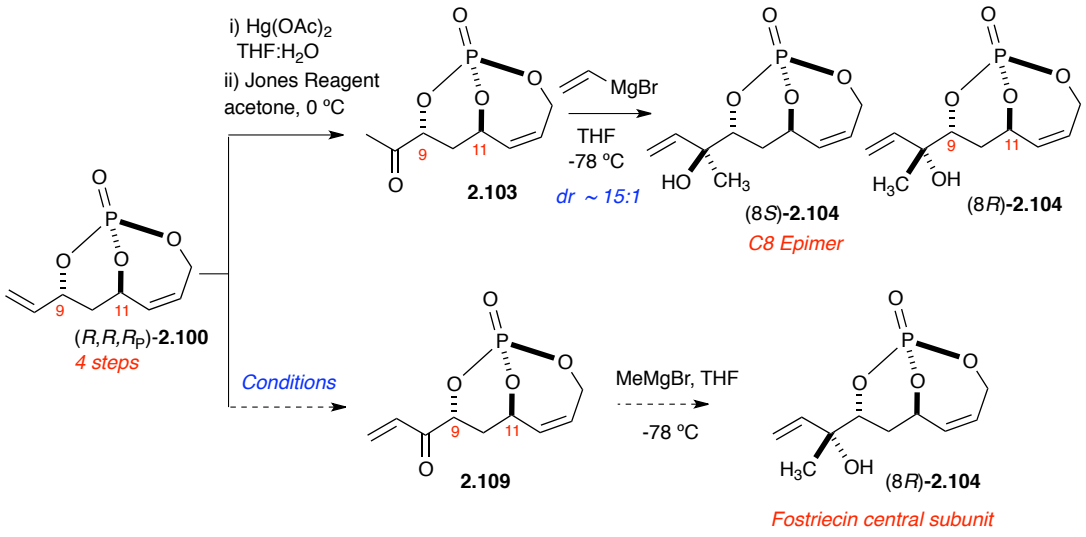
Use of vinyl ytterbium–generated from vinyl magnesium bromide and ytterbium trichloride [33] was next studied and showed that additions to the ketone carried out at -78 ºC afforded the C8 epimeric product exclusively (50:1 ratio) in 77% yield (Table 1, entry 6). Based on these empirical observations, we propose that the

vinyl group addition may occur in an intramolecular fashion (Scheme 10, **2.108**) while chelating to the oxygen atoms of the ketone and the phosphate. Vinyl Grignard addition in the presence of HMPA and DMPU further supported this assumption reducing the ratio towards the C8 epimer to 5:1 and 4:1 respectively. However, use of a vinyl cerate gave the highest ratio of the desired target (8*R*)-**2.104** with a selectivity of 1:2 (C8:C8-*epi*) (Table 1, entry 12). Furthermore, vinyl cerate addition to ketone **2.103** using THF:HMPA (2:1) afforded the best ratio for the expected product formation as 1.0:1.5 (C8:C8-*epi*). A plausible explanation for this observation is the higher nucleophilicity and larger ionic radii of the vinyl cerium complexes.[32]

Even though it is understood that non-chelating reagents would provide for better selectivity, lithium reagents could not be tested in this reaction, since all organolithiums tested were prone to attack presumably at phosphorus.[34] Furthermore, none of the organozinc additions that were studied, including those in the presence of organo-catalyst,[35] gave addition to the ketone, but rather unreacted starting ketone was recovered in all cases. Surprisingly, TMS-acetylene addition[36] also resulted in no reaction. Additional studies are still in progress.

Realizing that merely switching the "nature" of ketone and Grignard reagent would generate the desired C8 stereocenter, studies were next focused on the synthesis of vinyl ketone **2.109** using methyl Grignard addition into vinyl ketone **2.109** (Scheme 11).

Scheme 11



2.2.2.1 Synthetics studies to vinyl ketone

The synthesis of vinyl ketone was expected to be readily accomplished by employing several conditions, *vide infra*. Attempts were first focused on generation of vinyl ketone through vinyl Grignard addition to a C8 aldehyde intermediate, or C7/C8 terminal epoxide opening with dimethylsulfonium methylide ($Me_2S^+CH_2^-$)[37] which was anticipated to be synthesized from dihydroxylated bicycle-phosphate (*R*,*R*,R_P)**-2.100** (Scheme 12). Thus dihydroxylation of exocyclic double bond was next studied. To our delight, dihydroxylation of exocyclic olefin of (*R*,*R*,R_P)**-2.100** was successfully achieved using Sharpless conditions with ADmix-β in *t*-BuOH:H_2O (1:1) in excellent regio-and chemo-selectivity (*dr* = 15:1) but in moderate yields (Table 2, entry 1).[38] However, by employing Upjohn dihydroxylation conditions (OsO_4, NMO), the reaction was completed in good yield

(65 %) in 10–20 hours at 10 ºC, and the product **2.110** was produced with moderate diastereoselectivity (*dr* = 4:1) (Table 2, entry 2).[39] It should be noted that chemoselectivity was varied depending on the temperature. Dihydroxylation of both *exo*- and *endo*-cyclic olefins was observed if the reaction was performed at room temperature, while it was totally selective to the C7/C8 exocyclic olefin at 0 ºC. Additional studies carried out with metathesis catalyst demonstrated that chemoselective dihydroxylation can also be achieved with G-II in the presence of $PhI(OAc)_2$ and Lewis acid ($YbCl_3$ or $CeCl_3$) (Table 2, entry 6, 7, 8). This result

Scheme 12

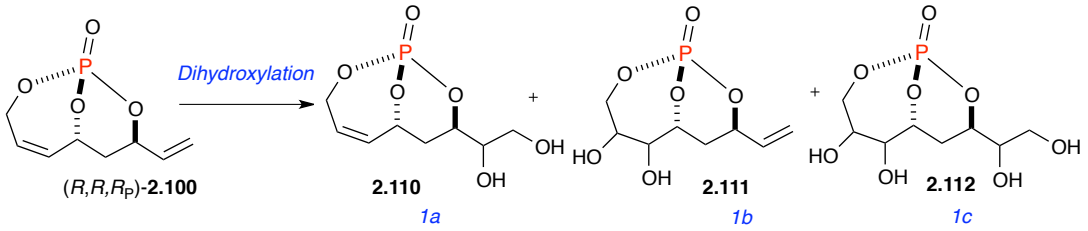


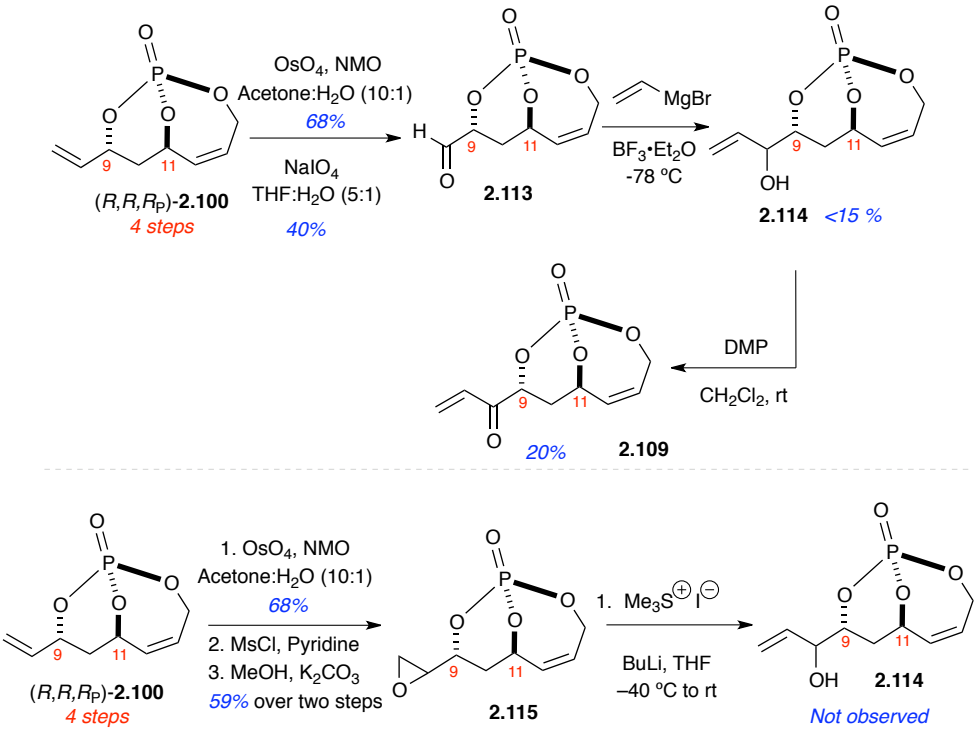
Table 2

Entry	Reagent	Time	Product	Yield (unoptimized)
1	Admix β	48 h	1a	36%
2	OsO_4 (2 mol %), NMO(2 eq) Acetone: H_2O(9:1), 10 ºC	8h	1a and 1b*	65%- 1a <10% 1b
3	Grubbs I , $CeCl_3 \cdot 7H_2O$, $NaIO_4$	5 h	1a and 1c	N.D.
4	Grubbs II, $CeCl_3 \cdot 7H_2O$, $NaIO_4$	5 h	1a and 1c	N.D.
5	Hoveyda–Grubbs II, $NaIO_4$, $CeCl_3 \cdot 7H_2O$	5 h	1a and 1c	N.D.
6	Grubbs I, **$PhI(OAc)_2$**, $YbCl_3$	24 h	**1a**	55%
7	Grubbs II, **$PhI(OAc)_2$**, $YbCl_3$	24 h	**1a**	58%
8	Grubbs II, **$PhI(OAc)_2$**, $CeCl_3 \cdot 7H_2O$	24 h	**1a**	64%

Ru Carbene(2 mol %), MCl_3 (10 mol %) Oxidant(2 eq) M=Ce, Yb

indicates that a potential chemoselective, one-pot protocol for RCM/dihydroxylation could also be employed, and efforts along these lines are currently underway. It should be noted that examples of Ru-catalyzed, one-pot protocols for chemoselective dihydroxylation are notably absent in the literature.[40] With these developed conditions in hand, synthesis of desired vinyl ketone was next studied via synthesis of aldehyde followed by vinyl Grignard addition (Scheme 13). Oxidative cleavage of dihydroxylated product **2.110** (Scheme 12) with $NaIO_4$ followed vinyl Grignard addition and subsequent oxidation afforded the requisite vinyl ketone **2.109**, but in very low yield. While optimization of this sequence is still being investigated, studies were next focused on epoxide opening with dimethylsulfonium methylide generated

Scheme 13

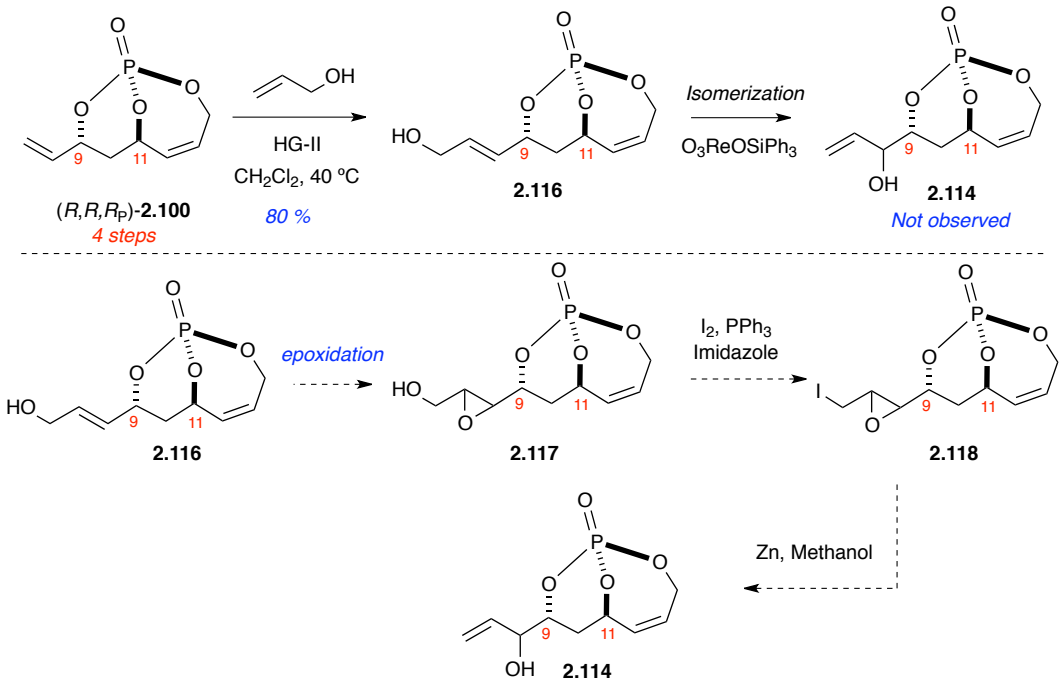


from *n*BuLi addition to Me_3S-I (Me_3S-I, *n*BuLi). Even though, direct epoxidation of the exocyclic double bond with *m*-CPBA was not promising, reaction with mesyl chloride followed by treatment of the resulting crude sulfonate with K_2CO_3 in MeOH afforded the requisite epoxide **2.115** in good yield (59 % for 2 steps). It should be noted that K_2CO_3/MeOH did not affect the phosphate group. However, the homologation of this epoxide with dimethylsulfonium methylide in THF to the desired allylic alcohol was not successful. [**Note:** It is assumed; nucleophilic addition of dimethylsulfonium methylide to the electrophilic phosphorus atom would also be possible and would be the reason for the observed-degraded products].

Having difficulties with the generation of vinyl ketone from either aldehyde **2.113** or epoxide **2.115**, studies were directed toward the isomerization reactions of allylic alcohol **2.116** generated from CM between (*R*,*R*,R_P)**-2.100** and allylic alcohol. However, this allylic isomerization with different Re-mediated catalysts (Re_2O_7, $O_3ReOSiPh_3$) also did not provide the required product **2.114**. Thus, studies will next be on the 3-step sequence as illustrated in Scheme 14.

While studies are still ongoing to develop an efficient synthesis of vinyl ketone **2.109**, installation of C1–C5 lactone functionality to the central core of fostriecin via CM was thoroughly examined. Both vinyl lactol **2.97** and vinyl lactone **2.98** were utilized in these studies. Their preparation is outlined below.

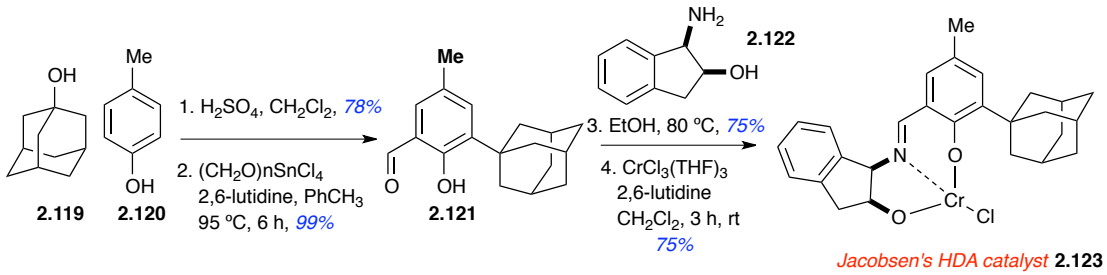
Scheme 14



2.2.2.2 Synthesis of vinyl lactol 2.97 and vinyl lactone 2.98

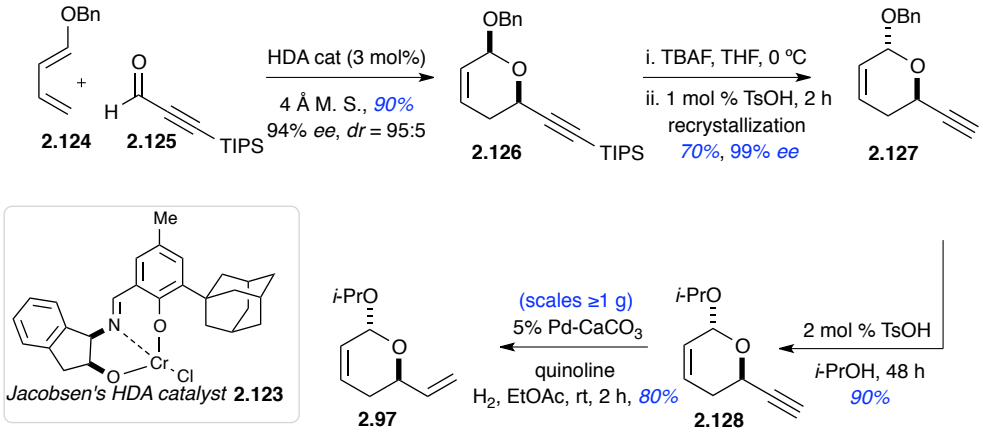
The desired vinyl lactol **2.97** and vinyl lactone **2.98** were generated utilizing the Jacobsen hetero-Diels-Alder method.[41] The sequence was initiated with generation of the pre-catalyst **2.123**, following the reported protocol by Jacobsen and coworkers (Scheme 15). Friedel-Crafts adamantylation of *p*-cresol followed by formylation via electrophilic addition of formaldehyde and subsequent oxidation by excess formaldehyde through a Oppenauer-type[42] oxidation generated aldehyde **2.121**. After the condensation reaction with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**2.122**), the resulting ligand was treated with $CrCl_3(THF)_3$ complex to afford the HDA catalyst **2.123**.

Scheme 15



Treatment of diene **2.124** and TIPS-protected aldehyde **2.125** in the presence of HDA catalyst **2.123** provided alkyne-lactol **2.126** in 90% yield. Desilylation, followed by isopropylation of benzyl acetyl alkyne lactol **2.127**, generated isopropyl-protected alkyne lactol **2.128.** Subsequent Lindlar hydrogenation with Pd-$CaCO_3$ in the presence of freshly distilled quinoline in EtOAc under H_2, afforded alkene lactol **2.97** in 80% yield on gram-scale (Scheme 16).

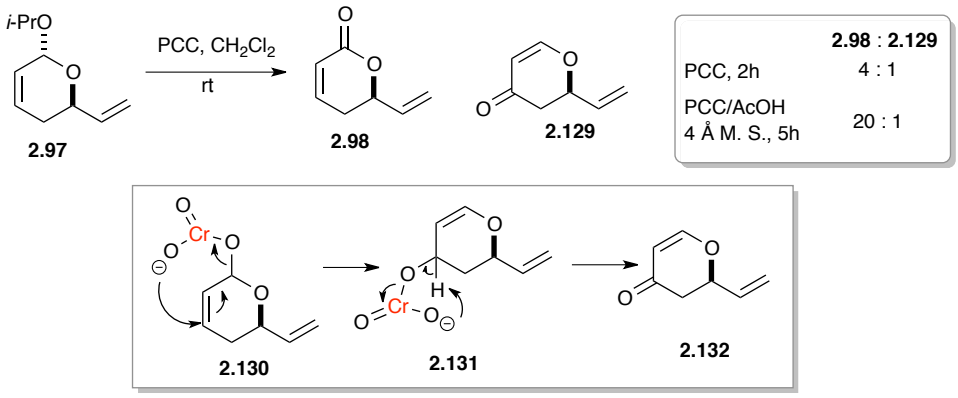
Scheme 16: *Formation of the Desired Cross-Metathesis Partner.*



The required vinyl lactone **2.98** was obtained in good yield via direct oxidation of the isopropyl acetal **2.97** with PCC in CH_2Cl_2 in the presence of AcOH

(Scheme 17).[43] When only PCC was used with Celite® in CH_2Cl_2, the vinyl lactone **2.98** and the rearranged product **2.129** were formed in 4:1 ratio with 80% overall yield over a 2 hour period. However, addition of 2 equivalents of AcOH decreased the formation of the rearranged product **2.129** and the vinyl lactone **2.98** was obtained in 83% yield in 5 hours. This prolonged reaction time, as well as the diminished amount of rearranged product formation, suggested that the presence of Lewis acidic reagent (AcOH, SiO_2, $CaCO_3$) in the reaction medium reduced the nucleophilicity of the oxyanion, which would initiate the rearrangement.

Scheme 17

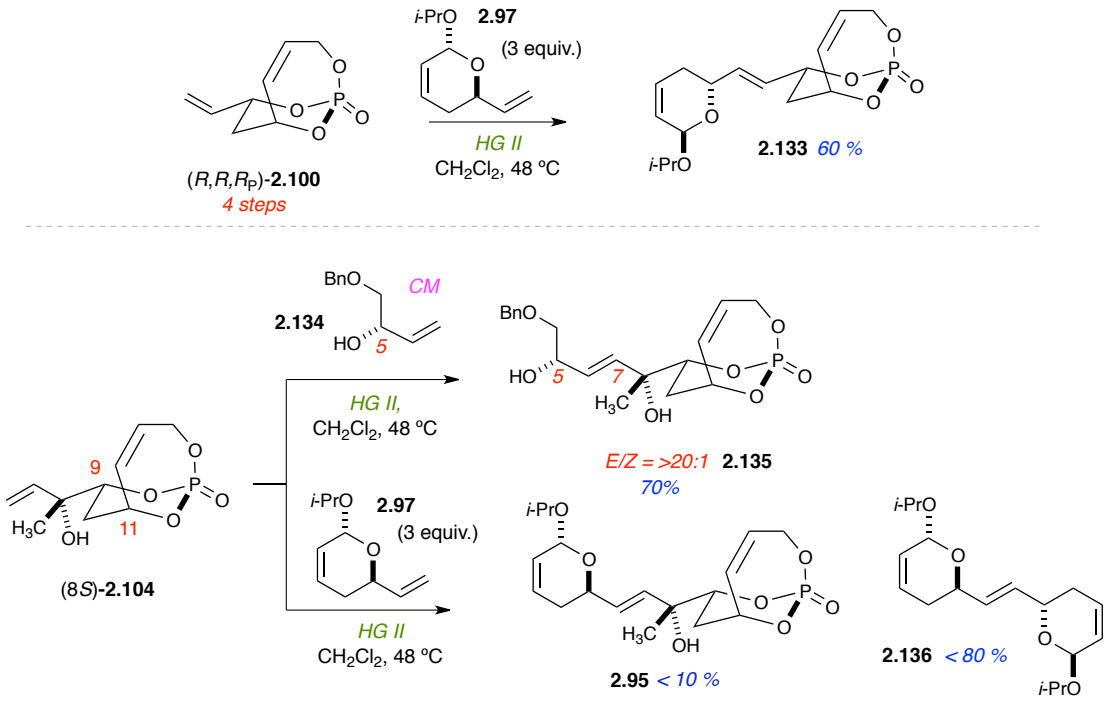


2.2.2.3 Cross-Metathesis (CM) studies with isopropyl lactol 2.97 and lactone 2.98

Initially, promising CM studies were carried out using the bicyclic phosphate *R*,*R*,R_P-**2.100** containing the terminal C7/C8 olefin with lactol **2.97** afforded **2.133** in 60% yield (Scheme 18). This result augmented previous reports in our group of successful CM between the C8-unprotected, bicyclic phosphate (8*S*)-**2.104** [C8-epi]

with the acyclic, allylic CM partner **2.134** to derive **2.135** in good yield and with excellent C6/C7 stereoselectivity (Scheme 18).[44] However, attempted coupling of phosphate (**8*S*)-2.104** and lactol **2.97**, while initially showing promise (in the absence of CuI), did not succeed as expected, and dimerized lactol product **2.136** was generated in large amounts with only small amounts of coupled product **2.95**. Use of an excess amount of lactol, change of solvent and the concentration as well as a longer reaction time did not improve the yield of this reaction.

Scheme 18

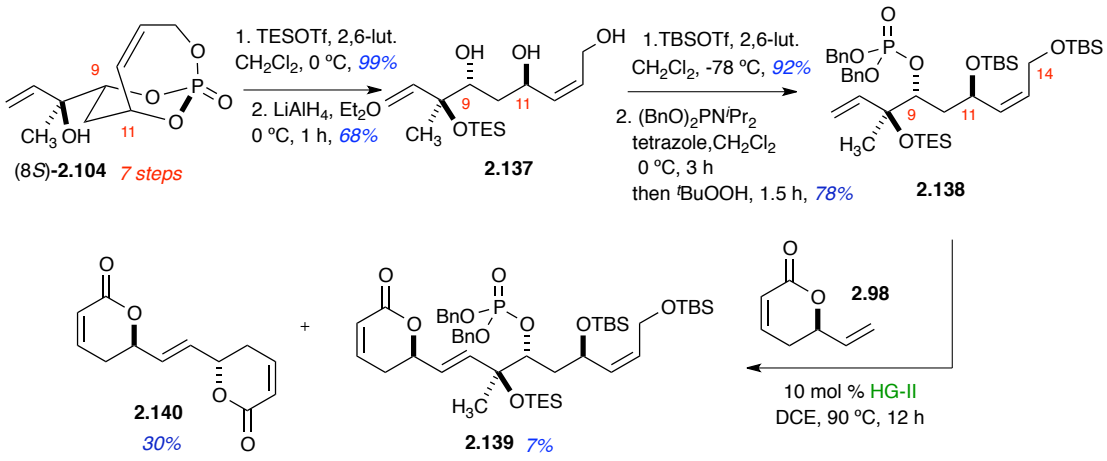


It was postulated that the electron withdrawing nature of the phosphate, as well as the presence of the allylic quaternary center, resulted in a less reactive exocyclic olefin towards CM, ultimately dictating rapid dimerization of the reactive lactol. At this juncture, efforts were temporarily directed toward CM studies of the

acyclic C6–C14 subunit, before returning at a later stage to the phosphate-tethered system, *vide infra*. It should also be noted, that all studies to this stage were performed in the absence of CuI, with CuI-promoted studies soon to prove quite pivotal in this story.

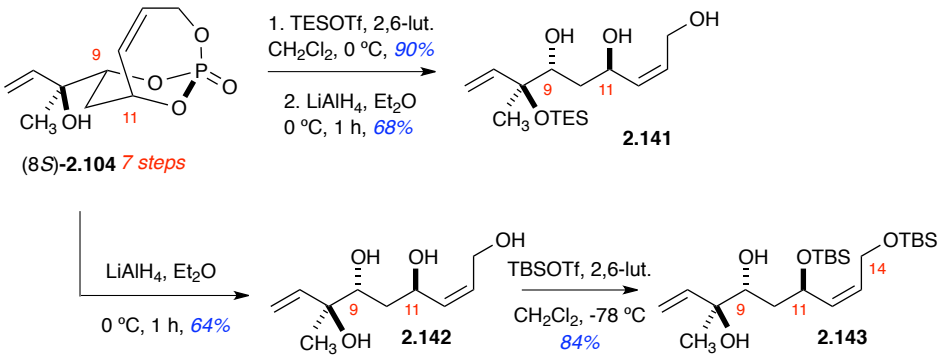
Initial CM studies without the phosphate tether were carried out using the acyclic core fragment **2.139**, which was prepared as outlined in Scheme 19.[44] Cross-metathesis of **2.98** with **2.139**, proceeded with good *E*-selectivity, but in very low yield. This yield was not improved, despite several changes in solvent, concentration, and catalyst (Scheme 19). In addition, the production of varying amounts of lactone dimer **2.140** in these CM studies, suggested that the lactone olefin does not possess typical type II olefin behavior, but instead is acting as a sluggish type II olefin.[45] Based on these empirical observations, efforts were next directed toward altering the olefin reactivity of both CM partners.

Scheme 19



In order to increase the reactivity of the lactone fragment, CM studies were directed toward installation of the more reactive isopropyl-protected lactol **2.97**. In addition, initial studies were carried out on the completely deprotected-triol fragment **2.141**, bearing a C8-TES-protected carbinol in order to probe the potential impact of the C9 phosphate. The synthesis of **2.141** (Scheme 20) commenced from the Grignard adduct (8*S*)-**2.104** and involved an initial TES-protection of the C8 tertiary alcohol, followed by tether removal with $LiAlH_4$ to produce triol **2.141**, primed for CM. In addition, we concurrently generated the unprotected, tertiary, allylic C8-alcohol-containing substrate **2.143** to examine the reactivity differences between C8-TES-protected substrate **2.141** and C11/C14-TBS-protected substrate **2.143** with the previously reported results for the fully protected acyclic phosphate **2.138** previously outlined in Scheme 19.

Scheme 20

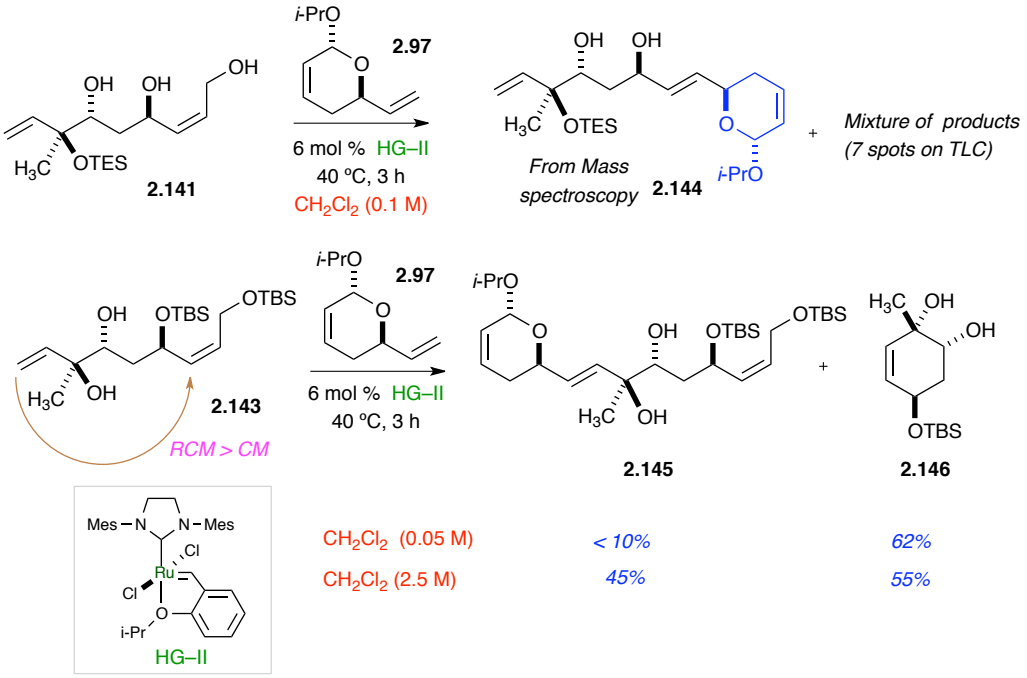


The unprotected tertiary alcohol substrate **2.143** was synthesized via an equivalent route where phosphate (8*S*)-**2.104** was directly subjected to tether removal with $LiAlH_4$ in Et_2O to produce tetraol **2.142**. Utilizing the precedent set by

Hatakeyama,[16] **2.142** was then subjected to selective *bis*-TBS-protection of the less sterically hindered C11 and C14 carbinols with TBSOTf at -78 ºC to cleanly generate the central core segment **2.143** (Scheme 20).

The initial CM studies of triol **2.141** and lactol **2.97** were conducted in CH_2Cl_2 at 0.1 M concentrations employing the Hoveyda-Grubbs second-generation catalyst (HG-II) [46] (Scheme 21). However, this resulted in a mixture of degradation products, revealed by thin layer chromatographic (TLC) analysis of the crude reaction mixture, as well as the identification of product **2.144** by mass spectral analysis, indicating that the CM was not initiated at the C6–C7 allylic terminal olefin, but instead at the internal disubstituted C12–C13 *Z*-olefin. These results further confirmed that TES-protection of the C8 carbinol was the main culprit for decreased reactivity in substrate **2.141**.

Scheme 21



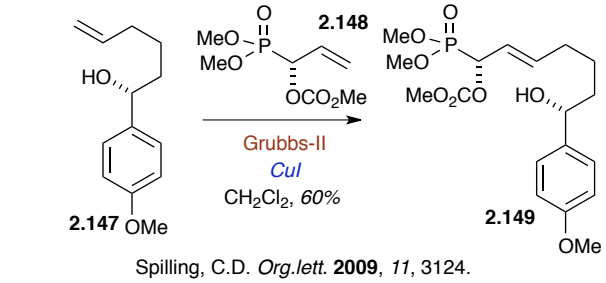
With these studies in hand, the acyclic substrate **2.143** was next investigated in CM studies with lactol **2.97**, whereby, the unprotected, C8-tertiary allylic alcohol would undoubtedly provide a more favorable environment to enhance the reactivity and selectivity of the C6–C7 terminal olefin (Scheme 21). In addition, studies set out to determine if TBS-protection of the C11 and C14 carbinols in **2.143** would impart enough steric hindrance to reduce the reactivity of the C12/C13 internal olefin to CM. While the CM issue with the C12/C13 olefin was circumvented, unfortunately the desired coupling product **2.145** was only obtained in 10% yield, while an undesired RCM product **2.146** predominated in 62% yield. To avoid RCM, the CM was run at higher concentration (2.5 M). In this case, as expected, CM did provide an increased yield of the desired CM adduct **2.145** in 45% yield however, it did not result in significant reduction in the formation of the RCM product **2.146**.

As the previous investigation outlined in Scheme 21 indicated, regioselective CM with the terminal C6/C7 olefin was complicated by RCM-reactivity with the internal C12/C13 *Z*-configured olefin, as well as the unforeseen CM-reactivity of the C12/C13 olefin. Of notable importance is the fact that these CM studies were in stark contrast to successful and clean CM reactions between the exocyclic double bond in the bicyclic phosphates *R*,*R*,*R*$_P$-**2.100** and *S*,*S*,*S*$_P$-**2.100** with numerous type 1 and type 2 olefins none of which resulted in any side reactions of the endocyclic *Z*-configured olefin.[23][47] Taken collectively, these CM studies revealed "another protective role" of the phosphate tether, which effectively prevents RCM of the external olefin with the internal *Z*-configured double bond. Based on these empirical

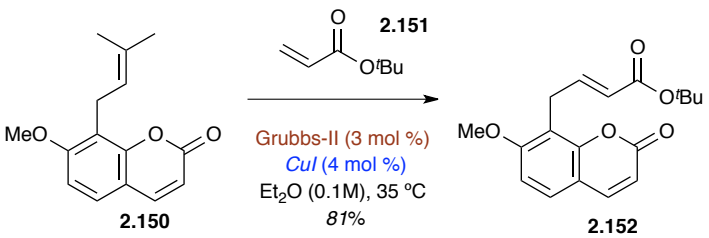
observations, studies were again focused on the bicyclic phosphate-containing vinyl Grignard adduct (8*S*)-**2.104**. However, these studies would employ use of CuI as an additive, *vide infra,* which was first reported by Blechert and coworkers in 2003.[48]

In 2004, Spilling and coworkers reported accelerated rates of sluggish CM reactions employing CuI as a co-catalyst.[49] In this method, they were able to derive phosphono allylic carbonates **2.149** via CM of alkenols **2.147** and acrolein-derived phosphono carbonates **2.148** (Scheme 22). In addition to phosphonate-containing substrates, CuI was also utilized in low-yielding CM reactions with substrates like acrylonitrile, vinyl ketone, acrylic acid that require higher catalyst load and heat.[50] Increased reactivity in this protocol was explained by the phosphine-sequestering effect of copper (I), which result in longer lifetimes of reactive open coordinate Ru-intermediates thus facilitating CM.

Scheme 22



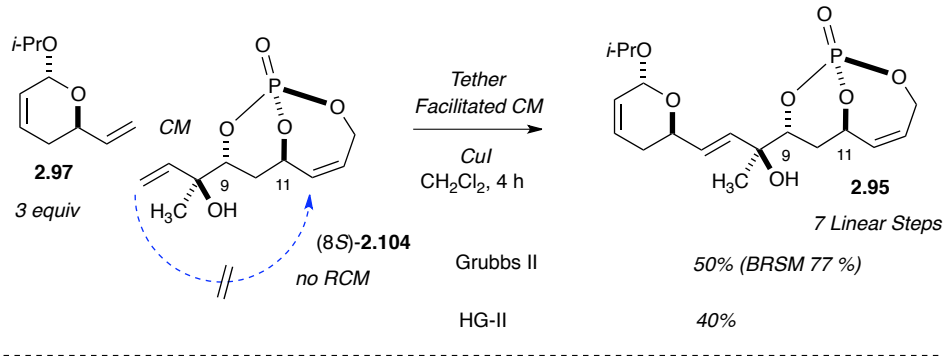
Spilling, C.D. *Org.lett.* **2009**, *11*, 3124.



Lipshutz, B. H. *J. Org. Chem.* ***2011****, 76, 4697*

Taking advantage of these precedents, CM was performed in the presence of CuI in CH_2Cl_2 in 2.5 M concentrations with Grubbs-II (Scheme 23). To our delight, CM product **2.95** was cleanly obtained in a much-improved isolated yield of 50% (77% BRSM). Furthermore, the unreacted phosphate SM (8*S*)-**2.104** was fully recovered. Overall, this CM route effectively enables the generation of the C1–C14 stereotetrad of fostriecin possessing the C6–C7 *E*-olefin and C12–C13 *Z*-olefin geometries in a 7 linear step sequence (LLS), which represents the shortest route to the C1–C14 stereotetrad-containing subunit when compared to all previously reported syntheses. In addition, as previously noted, this successful CM demonstrated a protective role of the phosphate tether, which effectively prevents RCM of the C6/C7 external olefin with the internal C12/C13 double bond.

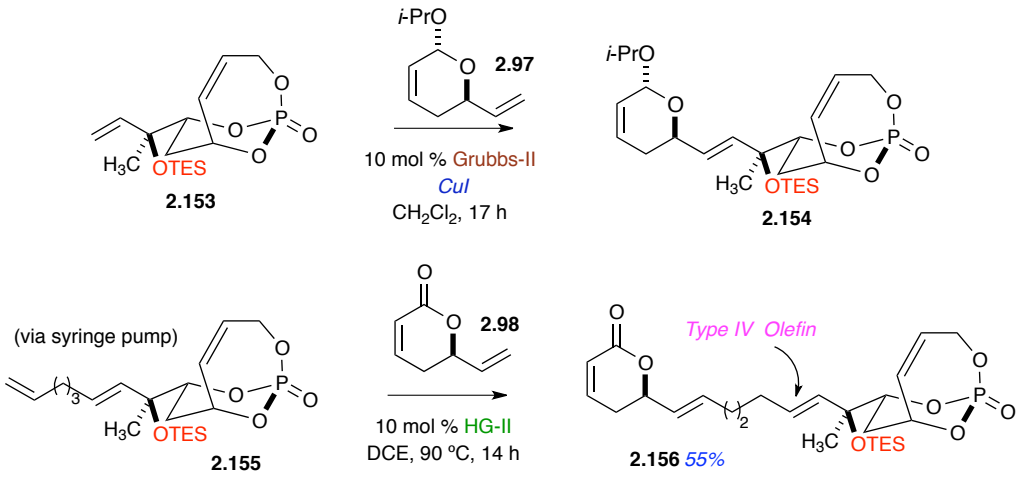
Scheme 23



Group	Linear Steps to *fostriecin*	Linear Steps to C5,8,9,11-stereotetrad	*Group*	Linear Steps to *fostriecin*	Linear Steps to C5,8,9,11-stereotetrad
Boger	27	19	*Imanishi*	25	13
Jacobsen	19	13	*Shibasaki (8-epi)*	25	15
Reddy	20	13	*McDonald*	16	10
Hatakeyama	21	16	*O'Doherty*	26	19

Despite this success, the separation of product **2.95** and the starting vinyl phosphate (8*S*)-**2.104** was still deemed problematic since it required TES-protection of the C8 carbinol in the crude reaction mixture to cleanly separate TES-protected product **2.95** from unreacted TES-protected starting material [(8*S*-TES)-**2.104**]. However, even though TES-protection allowed for clean separation, as previously noted, C8-TES protection imparts type IV olefin behavior and thus TES-removal was needed for the starting material to be recycled for use in subsequent CM (Scheme 24). It should be noted that this type IV CM behavior was further substantiated with relay partner **2.155**, previously carried out in our group,[44] whereby CM-relay was not seen, but instead provided CM product **2.156** as the major product (Scheme 24).

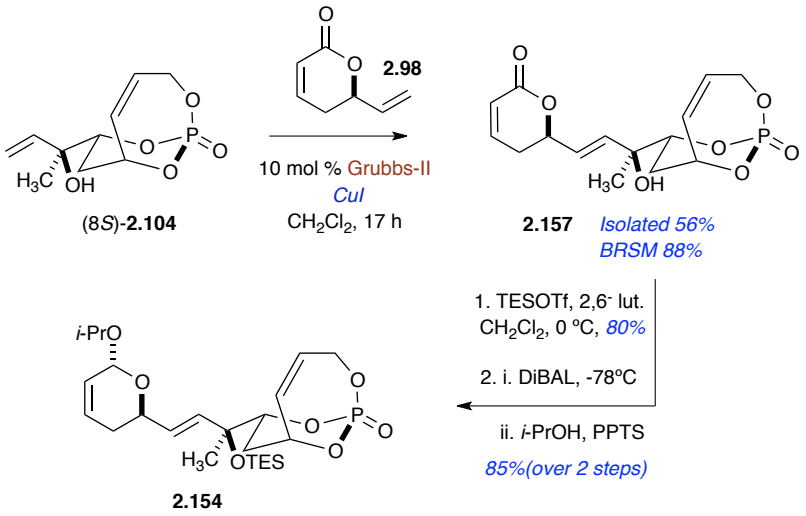
Scheme 24



CM reaction of lactone **2.98** and vinyl phosphate (8*S*)-**2.104** was next examined with the improved CuI addition protocol in order to potentially circumvent the aforementioned reusability issues of vinyl phosphate and separation issues with

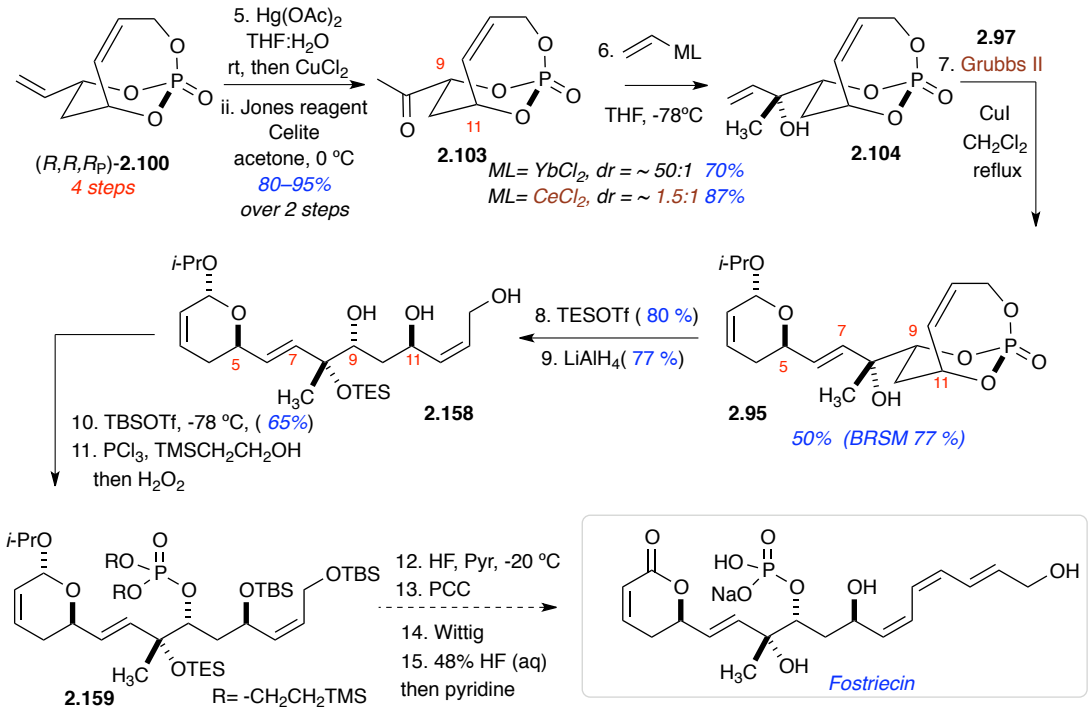
products and starting materials (Scheme 25). Very pleasingly, it was found that CM reaction between lactone **2.98** and vinyl phosphate (8*S*)-**2.104** provided well-separable products **2.157** and unreacted starting vinyl phosphate (8*S*)-**2.104** [TLC in EtOAc, **2.157**, R_f = 0.4; (8*S*)-**2.104**, R_f = 0.1] with only a small amount of the dimerized lactone by-product. An optimum isolated yield of 56% (BRSM 88%) was obtained via sequential addition of 0.3 equivalents of lactone **2.98** in 2-hour intervals in the presence of CuI and at 2.5 M concentration in CH_2Cl_2. Both HG-II and Grubbs-II catalysts provided equally good yields. Subsequent TES-protection of the isolated CM product, followed by DIBAL opening and mixed-acetal formation with isopropanol in the presence of a catalytic amount of PTSA afforded the requisite C1–C14 fragment containing all 4 stereogenic centers and olefin geometries (Scheme 25). Even though this route required two additional steps overall, i.e. (i) a one-pot

Scheme 25



protocol to convert the lactone **2.157** to the isopropyl-protected lactol **2.95** and (ii) a late-stage conversion back to the lactone, many added advantages were deemed important to enhancing the overall practicality of the route. These added benefits, included: (i) direct reusability of the starting vinyl phosphate, (ii) a higher yield, and (iii) reduction in the amount of dimer formation. In addition, success of this late-stage CM reaction showed the viability of this route in potential library development, *vide infra*.Having established a viable and effective route for both total and analogues synthesis, we set out to complete the total synthesis of fostriecin (Scheme 26). After TES-protection of CM adduct **2.95** with TESOTf and 2,6 lutidine at 0 ºC, the phosphate tether was removed under reductive conditions with $LiAlH_4$ in Et_2O at 0 ºC.

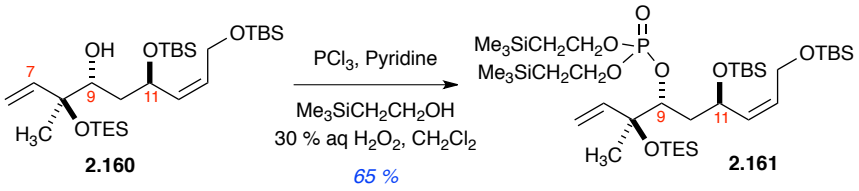
Scheme 26



The resulting triol **2.158** was subjected to selective *bis*-TBS protection at the C11 and C14 carbinols following a similar procedure that was discussed earlier.

Efforts were next directed towards installation of the phosphate group at the C9 hydroxyl, which we deemed orthogonal to all subsequent steps. Early-stage introduction of the C9 phosphate is in stark contrast to all previously reported synthetic routes to fostriecin that utilize late-stage installation of the phosphate as either a PMB-protected or allyl-protected phosphate ester. This strategy was adopted largely impart due to group experience with phosphate stability as well as literature precedent reported by Masamune and coworkers in synthetic studies to calyculin A (discussed in chapter 1).[51] In this study, they demonstrated the remarkable stability of a $Me_3SiCH_2CH_2$-protected phosphate over 12 consecutive steps, including hydrogenation, oxidation, Julia-Lythgoe olefination, and Stille coupling. Studies were therefore initiated with acyclic substrate **2.160** to introduce the $Me_3SiCH_2CH_2$-protected phosphate following the Masamune protocol to provide phosphate **2.161** in 65% yield (Scheme 27). At this stage, scale-up of this process is underway. Phosphate installation, followed by selective deprotection of the C14-TBS group, and subsequent oxidation with PCC will be used to install the requisite aldehyde that is armed for *Z*-selective Wittig olefination to introduce the eastern triene subunit (Scheme 26).

Scheme 27



2.2.3 Biological testing and library development.

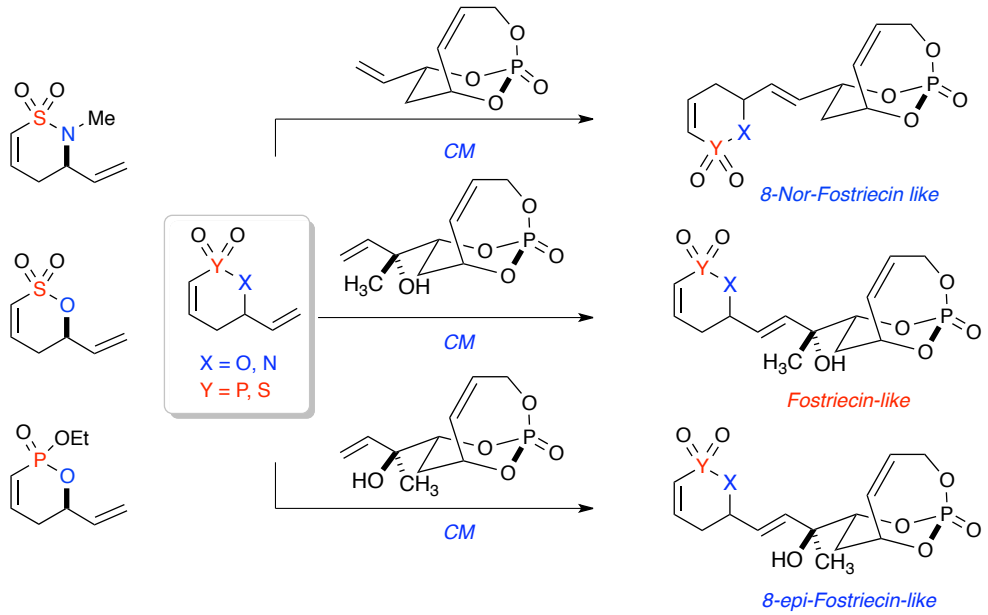
One of the long-term goals of this project is to develop new routes to access the "fostriecin-like" core subunits and thereby enable efficient analog generation. As explained in Section 2.1.2, clinical trials for fostriecin have been halted because of the stability (phosphate group) issues encountered with fostriecin, and analogues that were synthesized and tested did not meet the level of greater activity comparable to fostriecin. Despite enormous efforts by chemists and biologists, the continued search for more stable and potent fostriecin analogs that are more easily synthesized is still an enormous challenge.

As previously discussed, seminal SAR studies clearly showed that the C9 phosphate is a key structural feature in dictating potent activity against PP2A. In comparison to all literature reported routes, a major advantage of the route presented herein is the existence of cyclic phosphate intermediates throughout the synthesis (except for two intermediates), all of which represent new phosphate analogs for biological screening. Even though these phosphotriesters are not common in usual phosphotriester prodrugs (Chapter 1), they represent a potential solution for the low bioavailability of fostriecin. One such example of the high importance of our phosphate tether methodology is clearly demonstrated with ketone **2.103**, having

shown remarkable activity for the polo-like kinase (PLK1) assays out of 36,000 compounds. Detailed account of these biological hits will be reported in near future.

In addition to screening all intermediates in the synthetic pathway, we are currently focusing on the development of a fostriecin-like library using CM of modified lactone surrogates, with the goal of improving stability and selectivity for PP2A. The proposed library is shown in Figure 6. As the synthetic plan explains, incorporation of heteroatoms for the lactone carbonyl carbon should attenuate the Michael accepting nature of the western subunit.

Figure 6: *Proposed library for fostriecin.*

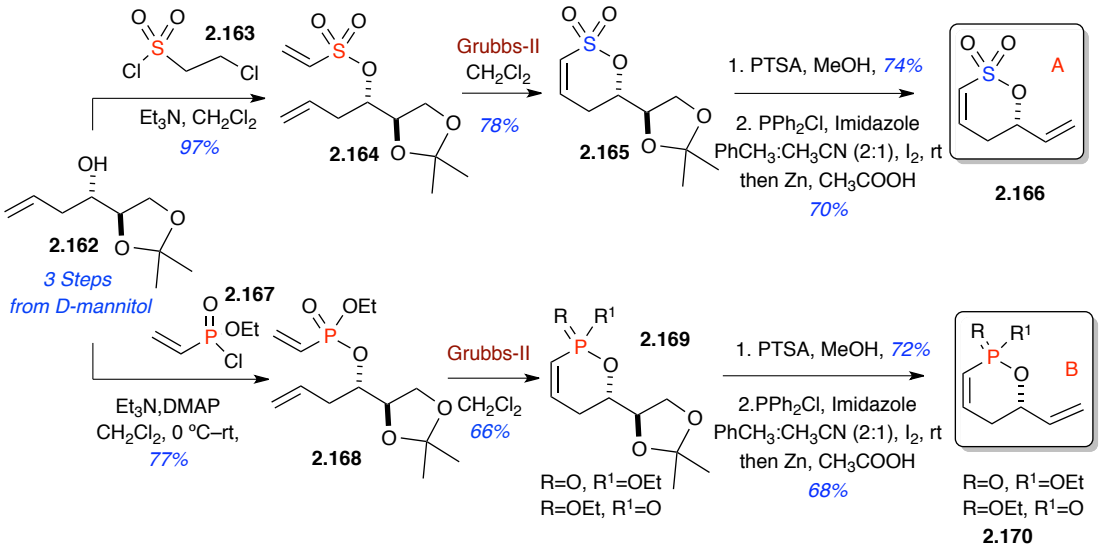


Synthesis of lactones began with generation of homo-allylic substrate **2.162** utilizing a known procedure;[52] starting from D-mannitol followed by $NaIO_4$ cleavage and subsequent allylation with Zn-mediated Barbier-type allylation in aqueous medium to provide **2.162** in 75% overall yield with good *anti* selectivity (*anti:syn* =

96:1, Scheme 28). It was reported that the high *anti* selectivity during the formation of alcohol is obtained as these reactions proceed *via* a Felkin-Anh model[53] rather than by a chelation-Cram model[54] since the water solvates the metal ions and thereby competes with the chelate complex.

Sulfonylation with sulfonyl chloride **2.163**, followed by RCM with Grubbs-II, provided sulfone **2.164**, which was subsequently subjected to a deprotection-elimination sequence to afford the lactone-coupling partner **2.165** (Scheme 28).

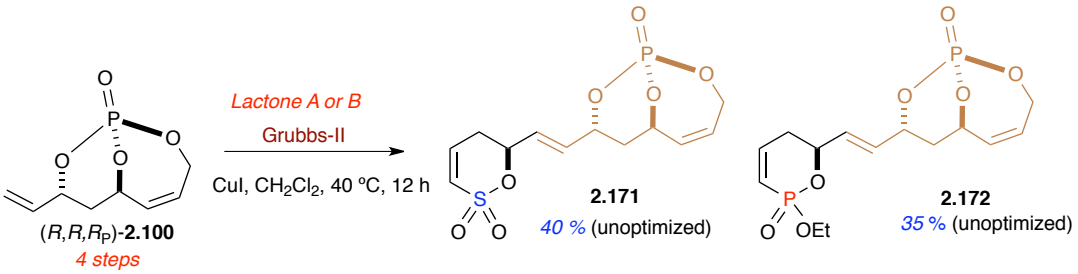
Scheme 28



A similar sequence was followed for the synthesis of phospho-lactone **2.170**, whereby vinyl ethyl phosphorochloridate **2.167** was used as the coupling agent. After phosphorylation and RCM with Grubbs–II catalyst, phosphor-lactone **2.169** was obtained and subsequently dehydrated to lactone **2.170** in 68% yield. After synthesizing the lactone-coupling partners, CM studies were performed with bicyclic

phosphate (R,R,R_P)-**2.100** and products **2.171** and **2.172** were obtained in moderate yield. With these encouraging results, studies will be continued with C6–C14 fragment to complete the fostriecin-like library compounds. In addition, generation of diastereomeric analogs via CM with bicyclic phosphate (S,S,S_P)-**2.100** will also be synthesized in the future.

Scheme 29



2.3 Conclusions and future direction

A library amenable, concise, and efficient CM route has been established for the synthesis of both fostriecin and its C8-epimer. In addition to the latent leaving group ability and the protective role for C9, C11 and C14 triols, the distinct role played by electronically poor phosphate group in shielding C12–C13 *Z*-configured olefin in CM studies has also been discussed. Furthermore, as a result of the phosphate tether/RCM approach the requisite C12–C13 *Z*-configured olefin was established in a single step without any *Z* selective protocols (Z selective Wittig, Z selective alkyne reduction), which have been used in each and every reported synthesis. Final efforts to fostriecin and C8-*epi*-fostriecin, along with the library synthesis and SAR-guided library development for all active intermediates will be discussed in due course.

2.4 *References*

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Chapter 3

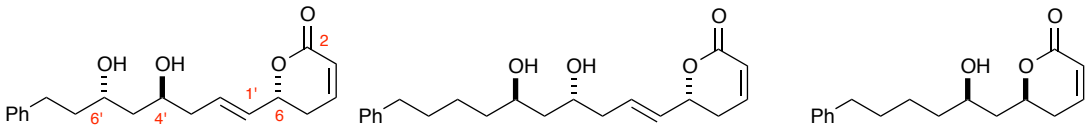
Total Synthesis of Strictifolione and

(6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one

3.1 Introduction:

The development of chemical methods that allow for the facile preparation of bioactive natural products and analogs is highly important to early phase drug discovery efforts aimed at improving human health. In particular, the discovery of drugs for the treatment of systemic antifungal diseases is highly important in light of the fact that over a million human deaths occur annually due to fungal associated diseases.[1] In addition, increasing mechanisms of resistance against current antifungal therapies, coupled with challenges with treating fungal infections of immune-compromised patients, warrant the search for new and improved therapeutic agents for combating fungal diseases.[2] This chapter describes the development of a synthetic route for facile preparation of the antifungal natural products, strictifolione (**3.1**) and a related natural product (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one (**3.2**), in a manner that is highly amenable to the production of analogs (Figure 1).

Figure 1: *Strictifolione and related natural products.*



Strictifolione (**3.1**) (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2*H*-pyran-2-one (**3.2**) Lactone monoalcohol **3.3**

3.1.1 Overview of strictifolione and related natural products:

(+)-Strictifolione (**3.1**) was isolated and structurally characterized by Aimi and coworkers from the stem bark of *Cryptocarya strictifolia*, a member of the family

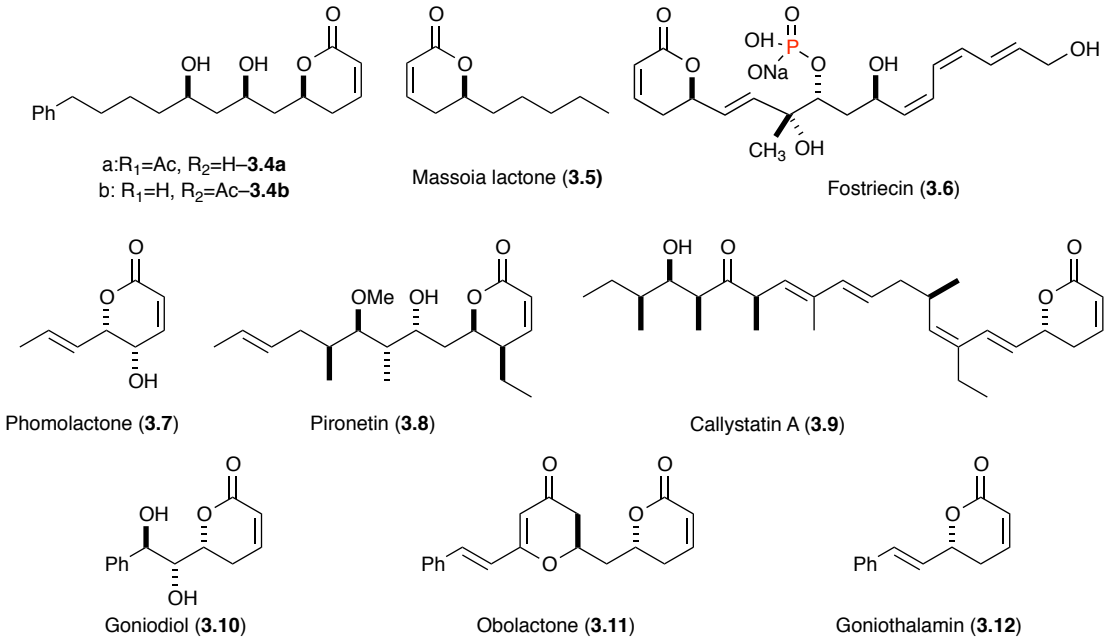
Lauraceae that grows in the rainforests of west Kalimantan, Indonesia.[3] The relative and absolute stereochemistry of **3.1** was proposed employing spectroscopic analysis. The relative stereochemistry of the C4'/C6' 1,3-diol functionality was elucidated from analysis of ^{13}C NMR chemical shifts of the acetonide derivative.[4] Of note is that the two methyl groups of the acetonide of the 1,3-*anti*-diol exhibited almost identical chemical shifts of 24.88 and 24.85 ppm, while in the corresponding 1,3-*syn*-diol, the characteristic methyl groups exhibited significantly distinct chemical shifts of 19.93 and 30.44 ppm.[3,4] In order to substantiate the acetonide analysis, the absolute configurations of their stereogenic centers were also determined utilizing Mosher analysis.[5] The structure of **3.1**, including the absolute configuration of all stereogenic centers, was further confirmed by Aimi and co-workers upon completion of the first total synthesis, employing (*S*)-malic acid and (*S*)-glycidol in 25 total steps and a longest linear sequence (LLS) of 18 steps.[6] Thereafter, various approaches for the synthesis of strictifolione have been reported in the literature.[7]

A related compound (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2-one (**3.2**), along with another structurally similar compound (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one (**3.3**) were isolated by Hostettmann and coworkers in 2001 from the leaves and bark of *Ravensara crassifolia* (Figure 1).[8] Krishna and coworkers accomplished the first total synthesis of **3.2** by iterative use of Jacobsen's hydrolytic kinetic resolution in 17 total steps and with a longest linear sequence (LLS) of 17 steps.[9] Interestingly, all three compounds (**3.1**–**3.3**) have been shown to possess antifungal activity.

Key structural features in **3.1** and **3.2** include a Michael-accepting 5,6-dihydro-α-pyrone moiety in the eastern subunit, a central 1,3-*anti*-diol, and lipophilic substitution in the western subunit. It is generally believed that the α,β-unsaturated pyranone functional group can react with the nucleophilic warhead of a target enzyme and thus attenuate its activity.[10] Moreover, structure-activity relationships (SAR) among different pyranone-containing molecules demonstrate that substituents on the side chain play a critical role.[10]

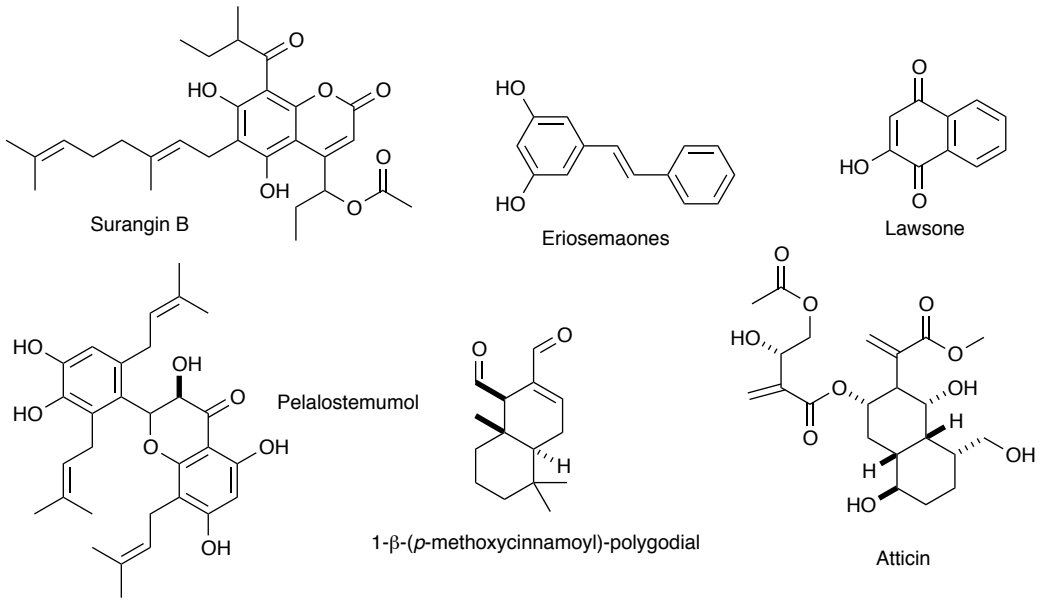
A number of natural products possessing the 5,6-dihydro-α-pyrone subunit with an accompanying C6 aryl-alkyl side chain, have been found to exhibit myriad biological activity and are outlined as follows (Figure 1).[11] Lactones **3.3**[8] and **3.4**,[12] as well as massoi lactone (**3.5**),[13] have been found to exhibit antifungal activity, while fostriecin (**3.6**) is a known anticancer agent with potent and selective inhibitory properties against PP2A.[14] Phomalactone (**3.7**) has shown herbicidal, antibacterial and insecticidal activity,[15] while pironetin (**3.8**) has been found to inhibit cell cycle progression in the M-phase.[16] Furthermore, callystatin A (**3.9**),[17] gonodiol (**3.10**)[18] and obolactone (**3.11**)[19] all exhibit cytotoxic activity, while goniothalamin (**3.12**)[20] induces apoptotic activity. Taken collectively, these attributes have prompted substantial interest in the total synthesis of compounds bearing the 5,6-dihydro-α-pyrone moiety.

Figure 1: *5,6-Dihydro-α-pyrone-containing natural products.*



In addition to the above-mentioned antifungal agents, there are several antifungal natural products whose structural frameworks differ widely, and which also lack the δ-lactone moiety.[21] Overall, the disparate array of structure, the inability of predicting key pharmacophores, the growth of life-threatening human fungal infections in immunosuppressed individuals, and the rising development of resistance to current drugs,[22] warrants continued investigations towards filling the unmet need for new antifungal drugs. Hence, there is still a high importance and urgency for the development of new antifungal compounds with improved properties. In particular, the development of a library-amenable synthetic route will aid in subsequent SAR and biological studies, while incorporating important structural features.

Figure 2: *Some examples for natural anti-fungal compounds*



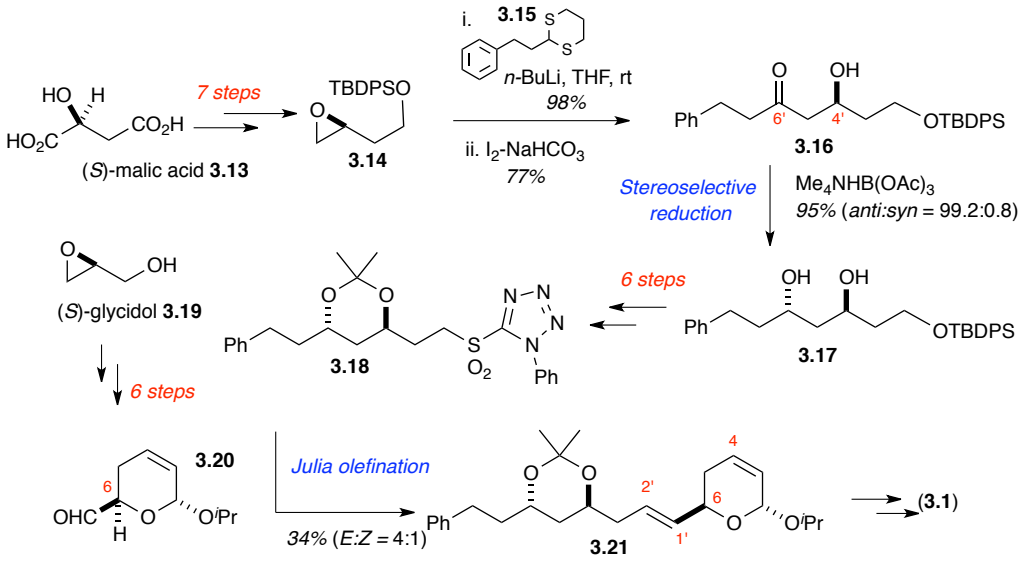
3.1.2 Overview of strictifolione synthetic strategies

After the seminal total synthesis of **3.1** by Aimi and coworkers, several elegant syntheses have been reported in the literature.[6,7] A brief overview of each synthesis will be discussed in this section, outlining key transformations employed in each approach to establish the requisite stereogenic centers as well as the olefin geometries.

As previously stated, in 2002, Aimi and coworkers reported the total synthesis of **3.1** using a synthetic pathway entailing a LLS of 19 steps.[6] The C4' and C6' 1,3-*anti*-diol were generated from the (*S*)-malic acid-derived epoxide **3.14** opening with the anion of dithiane **3.15**, followed by dithiane deprotection and subsequent stereoselective reduction of the resultant β-hydroxy ketone **3.16** with $Me_4NBH(OAc)_3$

(Scheme 1). The masked pyranone aldehyde **3.20** was synthesized from (*S*)-glycidol, employing the reported route by Crimmins and coworkers[23] in 6 steps and the C6 stereogenic center was derived (*S*)-glycidol. The C1′–C2′ *E* olefin geometry was obtained via the Kocienski-modified Julia olefination of masked pyranone aldehyde **3.20** with sulfone **3.18** in 34% yield and moderate selectivity (*E*:*Z* = 4:1).

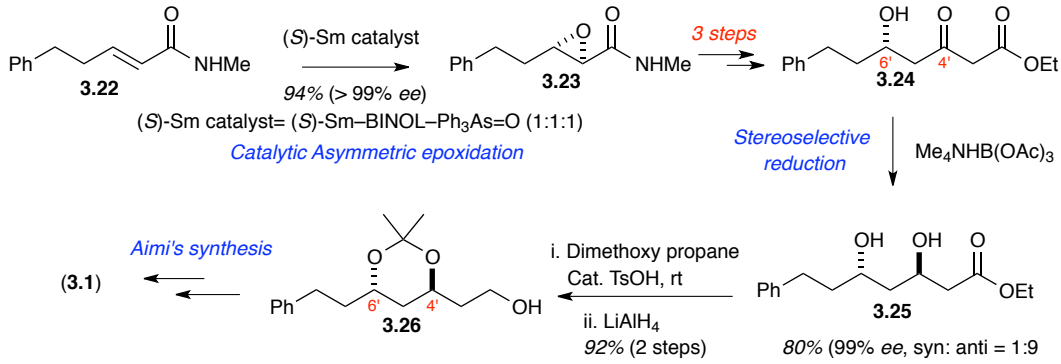
Scheme 1



In 2003, Shibasaki and coworkers reported synthetic studies to synthesize key intermediate **3.26**, employing a catalytic asymmetric epoxidation of α,β-unsaturated amide **3.23** utilizing a Sm–BINOL–$Ph_3As{=}O$ (1:1:1) complex.[7b] The resulting optically pure α,β-epoxyamide **3.23** was then transformed to γ,δ-epoxy β-keto ester and subsequent reductive epoxide opening with selenium reagent (prepared from PhSeSePh and $NaBH_4$)[24] afforded the C6′ carbinol containing γ-hydroxy β-keto ester

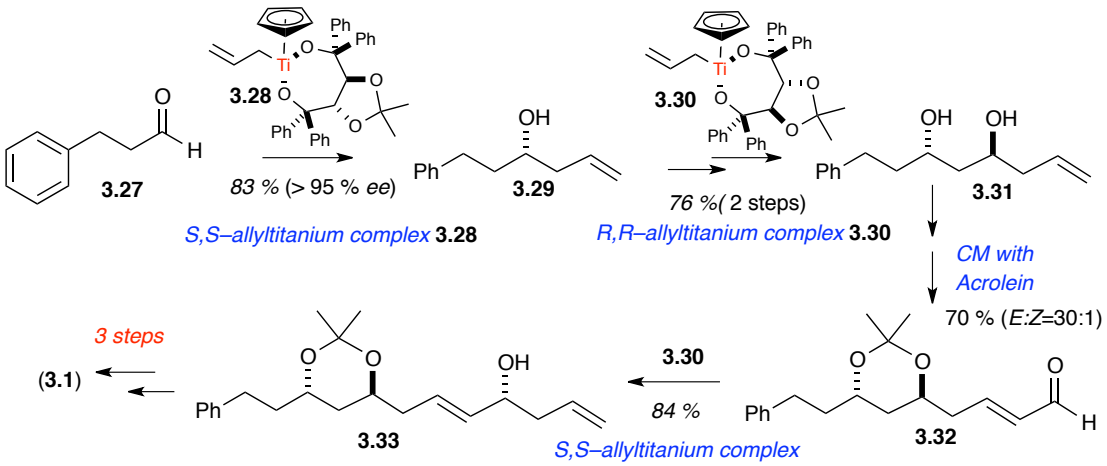
3.24 in good yield. The diastereoselective *anti* reduction of keto ester **3.24** with $Me_4NBH(OAc)_3$ [25] generated the 1,3-*anti*-diol-containing intermediate **3.25** possessing the requisite C4' stereogenic center in 79% yield and good selectivity (*syn*:*anti* = 1:9). Subsequent acetonide protection of diol followed by $LiAlH_4$ reduction of the ester functionality afforded the key intermediate **3.26** in 92% overall yield over 2-steps.

Scheme 2



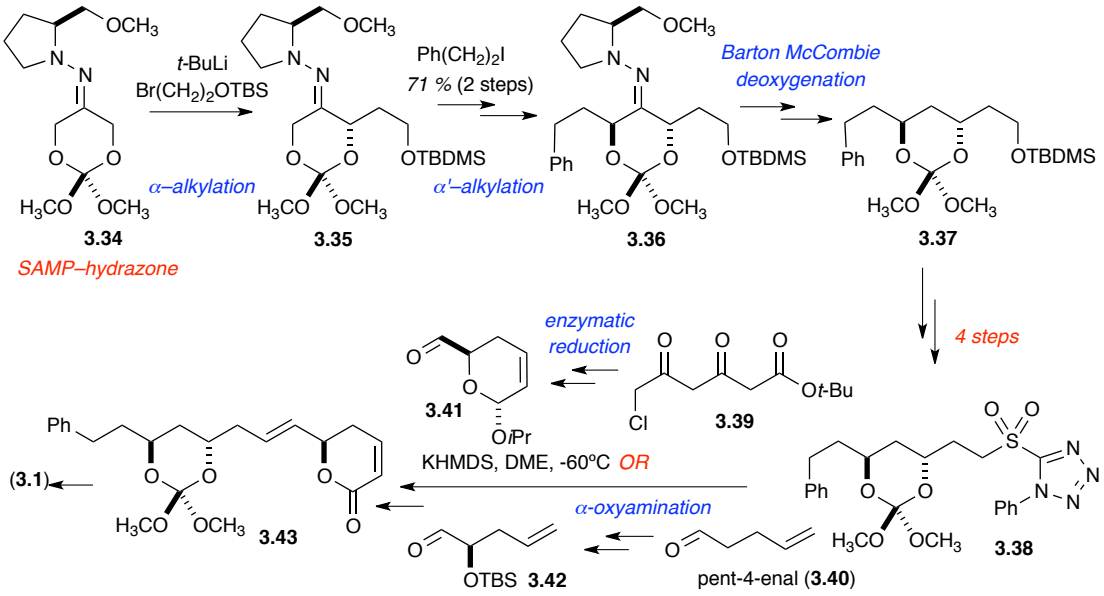
In 2003, Cossy and coworkers reported an efficient synthesis of **3.1** with 9 total steps, employing 3 enantioselective allyltitanations [26] starting from 3-phenylpropionaldehyde (**3.27)** to establish the stereogenic centers at C6, C4' and C6'. Cross-metathesis (CM) of the protected homoallylic alcohol with acrolein established the C1'–C2' *E*-configured olefin geometry (Scheme 3).[7a] The lactone subunit was constructed via esterification of homoallylic alcohol **3.33** with acryloyl chloride, followed by RCM.

Scheme 3



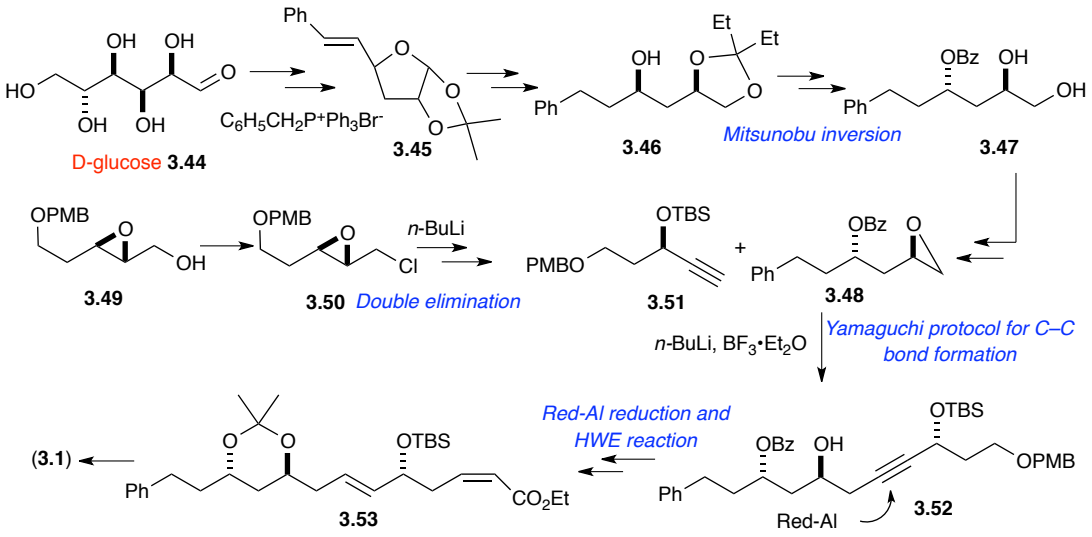
In 2004, the Enders group reported an asymmetric synthesis of strictifolione in 11 linear steps (Scheme 4).[7c] The highlight of this approach includes utilization of SAMP-hydrazone **3.34** in conjunction with α,α'-bis-alkylation/deoxygenation protocol to produce the C4'/C6'-*anti* diol subunit **3.37** (Scheme 4). Enzymatic reduction with baker's yeast was employed to establish the C6 stereogenic center in the subsequent preparation of the lactone unit **3.41** from the diketoester **3.39**.[27] Alternatively, (*S*)-proline-catalyzed α-oxyamination of pent-4-enal was used to introduce the requisite C6 stereogenic center within the lactone precursor, α-siloxy-substituted aldehyde **3.42**. The C1'–C2' *E*-configured olefin was introduced via Julia-Kocienski olefination[28] of sulfone **3.38** with aldehyde **3.41** or **3.42** in moderate yield (61%) and selectivity (*E*/*Z* = 8.5:1).[7c]

Scheme 4



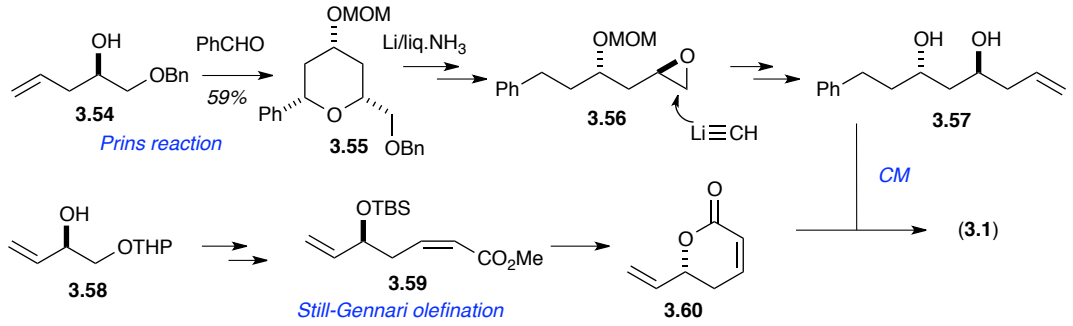
In 2005, the Ramana group reported the chiral pool synthesis of **3.1** from D-glucose in a route with a LLS of 19 steps (TS = 26).[7d] Mitsunobu inversion of **3.46** installed the C6′ carbinol of **3.47** (Scheme 5). The C2'–C3' bond formation employing Yamaguchi protocol[29] with lithium acetylide **3.51** and epoxide **3.48** C2′–C3′ afforded the advanced intermediate **3.52** in good yield (85%). The C1'–C2' *E*-configured olefin was installed via Red-Al® reduction of alkyne **3.52** and the employment of a *Z*-selective HWE olefination established the C3–C4 *Z*-configured olefin geometry.

Scheme 5



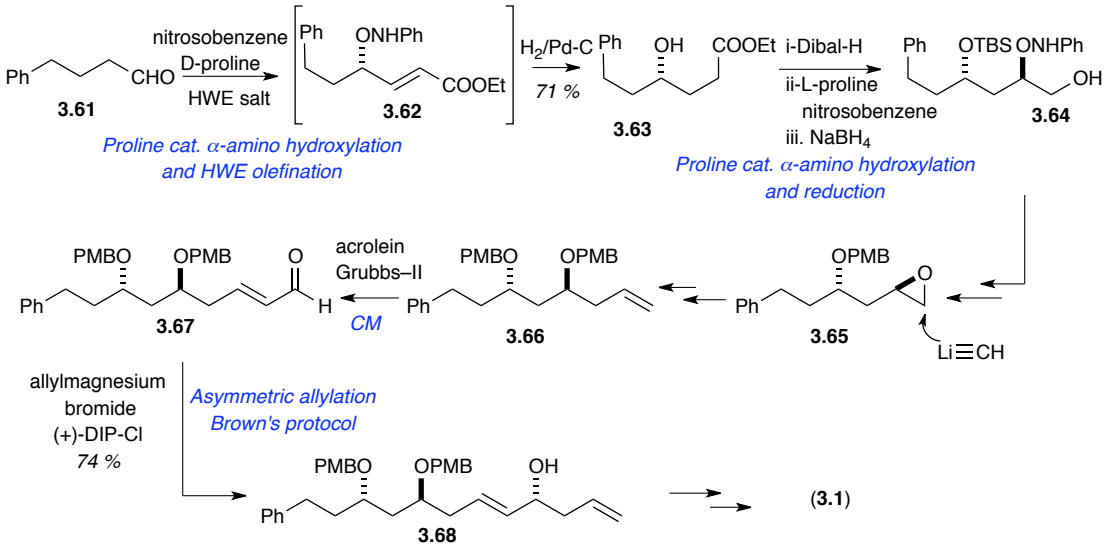
In 2009, the Sabitha group accomplished the total synthesis of **3.1** in a short route with a LLS of 10 steps (TS = 19).[7e] The highlight of this synthesis was utilization of an asymmetric Prins reaction of homoallylic alcohol **3.54** and benzaldehyde to generate the 1,3–*anti*-diol stereochemistry (Scheme 6). The MOM-protected tetrahydropyran **3.55** (generated from asymmetric Prins reaction) was opened with Li in liquid NH_3, which upon epoxidation, followed by Li-acetylide opening and subsequent Lindlar's reduction, provided the corresponding homoallylic alcohol **3.57**. The vinyl lactone **3.60** was synthesized in 5 steps, starting from homoallylic alcohol **3.58** utilizing HWE olefination to establish the C2–C3 *Z*-configured olefin geometry. The C1'–C2' *E* olefin geometry was installed via CM with vinyl lactone **3.60** and key fragment **3.57**.[7e]

Scheme 6



In 2010, Kumar and co-workers reported a 14-step synthesis of **3.1**.[7f] The key transformations utilized include, two enantioselective proline-catalyzed sequential α-amino hydroxylations[30] starting from the aldehyde **3.60** to obtain the 1,3-*anti*-diol subunit (Scheme 7). Subsequent Brown asymmetric allylation of **3.67** installed the stereogenic center at C6. Cross metathesis and RCM were utilized to produce the C1'–C2' *E*-configured olefin and the C3–C4 *Z*-configured olefin geometries,

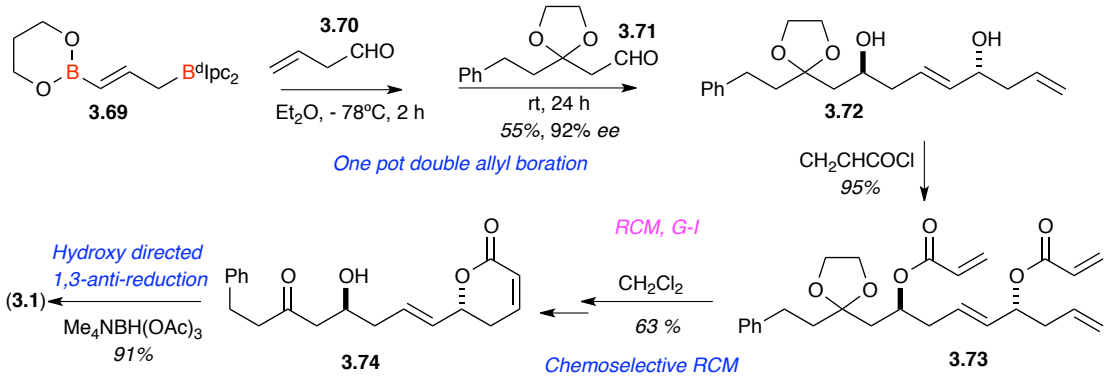
Scheme 7



respectively.[7f] In addition, as an alternative approach, the Jacobsen hydrolytic kinetic resolution was used to generate the 1,3-*anti* diol subunit as well as BINAL-H-mediated asymmetric reduction to obtain the C6 stereogenic center.[7f]

In 2010, She and coworkers accomplished the total synthesis of **3.1** in 9 steps utilizing a one-pot, double allyl boration reaction[31] of boryl-substituted allylborane **3.69** with aldehyde **3.70** and **3.71** to afford an enantio-and diastereoselective synthesis of (*E*)-1,5-*anti*-ene-diol **3.72** which contains the C4' and C6 stereogenic centers as well as the C1'–C2' *E* olefin geometry (Scheme 8).[7g] The C3–C4 *Z*-configured olefin geometry was generated via RCM of biacrylate tetraene precursor **3.73** using Grubbs 1st generation catalyst under high dilution conditions in refluxing CH_2Cl_2. Hydroxy-directed 1,3-*anti*-reduction of the *β*-hydroxy ketone **3.74** with $Me_4NBH(OAc)_3$ established the C6' stereocenter in good yield and with high *anti*-diastereoselectivity (91 %, dr = 96:4)

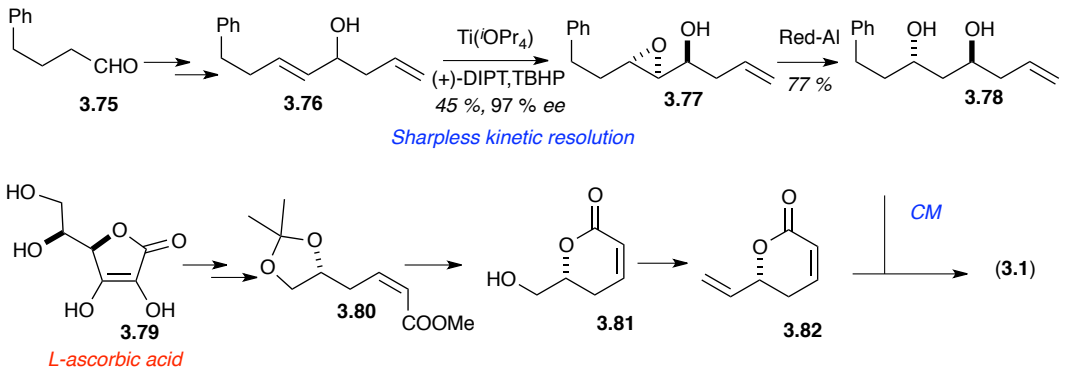
Scheme 8



In the same year, Das and co-workers achieved the synthesis of **3.1** with a

LLS of 10 steps and TS count of 15 steps.[7h] This approach entailed utilization of Sharpless kinetic resolution to furnish optically pure epoxy alcohol **3.77**. Subsequent epoxide ring opening with Red-Al generated the 1,3-*anti* diol fragment **3.78**. Vinyl lactone **3.82** was separately synthesized starting from L-ascorbic acid and the *Z*-olefin geometry was achieved via Still-Gennari-Wittig reaction. The (*E*)-configured C1'–C2' double bond was synthesized via cross metathesis with **3.78** with vinyl lactone **3.82**.

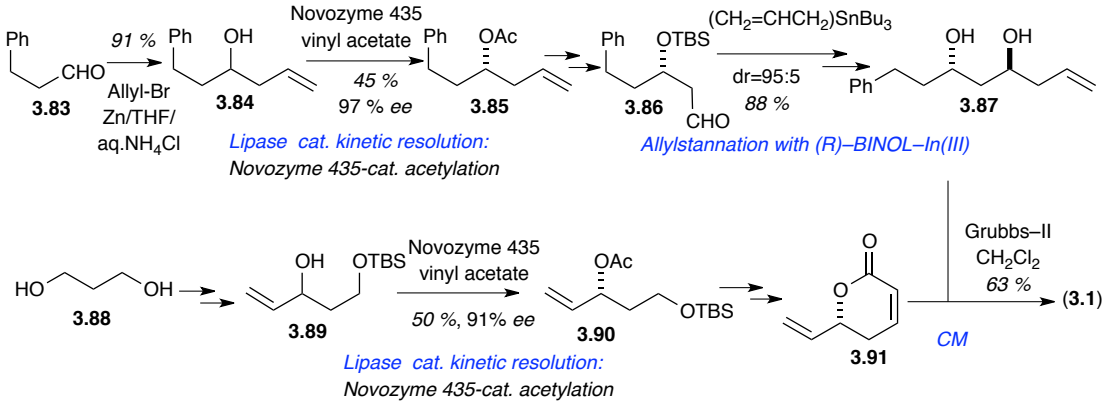
Scheme 9



In addition to these synthetic studies, in 2012, Sharma and coworkers reported the chemo enzymatic asymmetric synthesis of **3.1** utilizing lipase-catalyzed (Novozyme 435, *candida antarctica* lipase B immobilized on macroporous acrylic resin) acetylation to obtain both fragments **3.85** and **3.90** to establish the stereocenters at C6' and C6, respectively. An asymmetric allylstannation of **3.86** with allyl(Bu)$_3$Sn alongside a chiral In(III) catalyst (prepared from (*R*)-BINOL and $InCl_3$) established the C4' carbinol stereogenic center and furnished the 1,3-*anti*-diol subunit **3.87** in 88 % overall yield and excellent diastereomeric ratio (dr=95:5).[7i] *Z* and *E* olefin

geometries were produced with *Z*-selective HWE reaction and cross metathesis of vinyl lactone **3.91** and diol subunit **3.87**.

Scheme 10



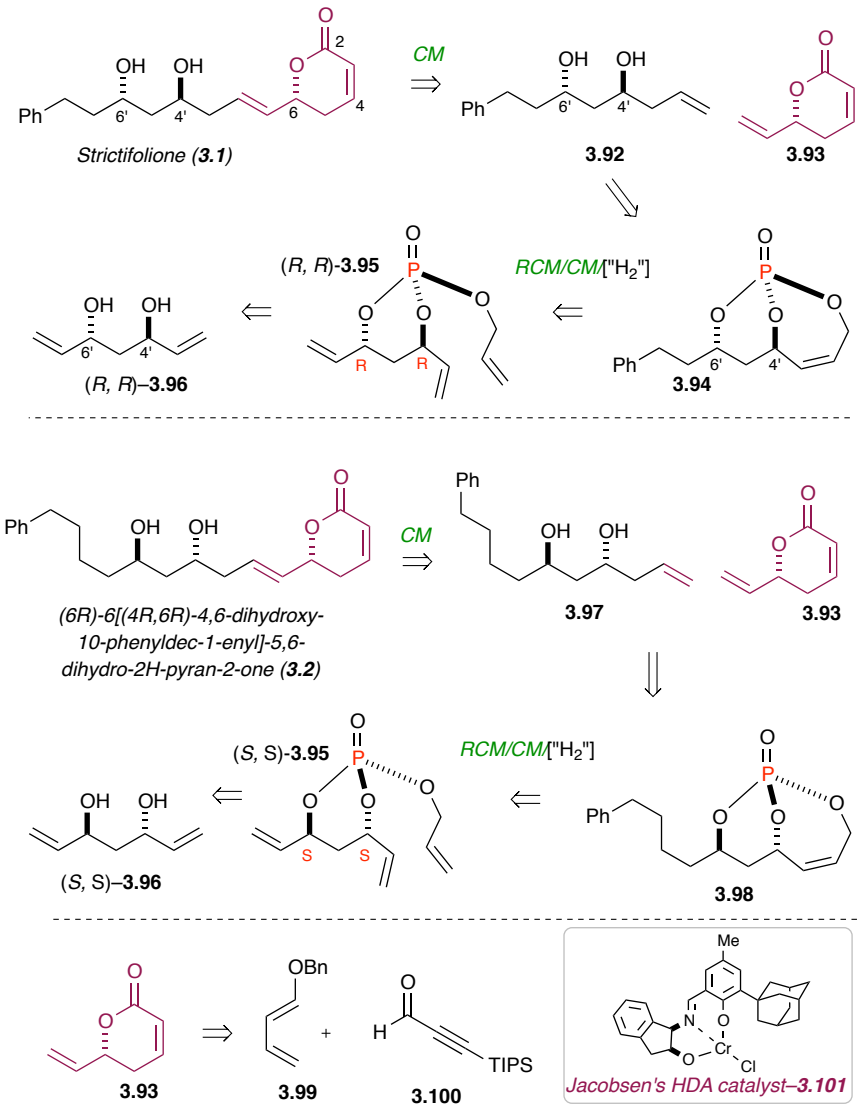
Among several elegant methods, Cossy, Das, and She were able to construct strictifolione (**3.1**) in efficient synthetic pathways with concise longest linear sequences of 9-, 10- and 9-steps, respectively. These syntheses of **3.1** are among the most efficient reported to date. Despite noted attributes of these syntheses,[7] the development of simple, efficient, and scalable strategies remains challenging and important. In this regard, multi-step one-pot protocols that facilitate total/intermediate/analog synthesis have emerged as powerful synthetic strategies, due to their ability to form multiple bonds and stereocenters, while invoking step, atom and green economy.[32,33] In the remainder of this chapter, we disclose an efficient, simple modular approach for the total synthesis of both naturally occurring antifungal compounds **3.1** and **3.2** that employes a phosphate tether-mediated one-pot, sequential, RCM/CM/chemoselective hydrogenation protocol.[34]

3.2 Results and discussion

3.2.1 Retrosynthetic analysis of (+)-strictifolione

Retrosynthetic analysis reveals that both natural products **3.1** and **3.2** can be readily derived from key diol-containing intermediates **3.92** and **3.97**, respectively, via CM with vinyl lactone **3.93** (Scheme 11). The pivotal diol **3.92** and **3.97** in turn can be synthesized from phosphates **3.94** and **3.98**, employing a regioselective Pd(0)-catalyzed reductive allylic transposition and phosphate tether removal under reductive conditions. The phenyl-substituted, bicyclic phosphate **3.94** can be synthesized from triene (*R*,*R*)-**3.95** via a one-pot, sequential RCM/CM/"H_2" with *cis*-stilbene as the CM partner, followed by chemoselective hydrogenation with *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH).[35] The triene (*R*,*R*)-**3.95** is readily prepared in 2-steps via sequential tripodal coupling of the C_2-symmetric *anti*-diene diol (*R*,*R*)-**3.96** and allyl alcohol with $POCl_3$, or in one step utilizing phosphoramidite chemistry.[36] Similarly, phosphate **3.98** can be synthesized following the same sequence of RCM/CM/"H_2" starting with enantiomeric triene (*S*,*S*)-**3.95** that is obtained from 1,3-*anti*-diene diol (*S*,*S*)-**3.96** utilizing phenyl-but-3-ene as a CM coupling partner. Vinyl lactone **3.93** can be readily derived from the Diels-Alder reaction of diene **3.99** and TIPS-protected propargyl aldehyde **3.100** employing the Jacobsen hetero Diels-Alder (HDA) catalyst.[37]

Scheme 11. *Retrosynthetic analysis of natural products **1** and **2**.*

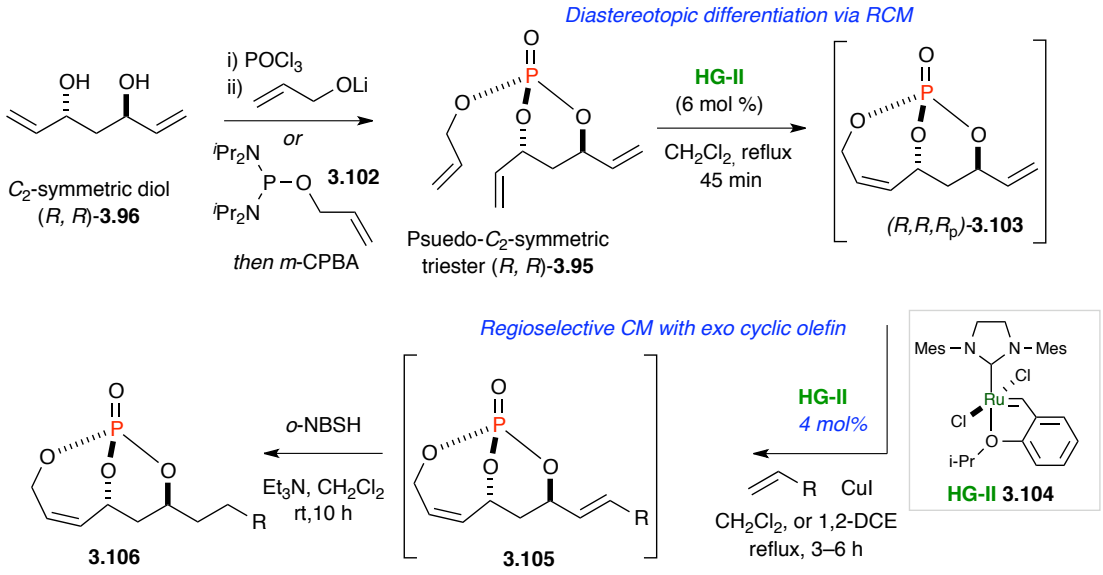


3.2.2 *Total synthesis of (+)-strictifolione and* (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-*2H*-pyran-2-one

The key starting substrate phosphate triester (*R*,*R*)-**3.95** was synthesized from tripodal coupling of C_2-symmetric 1,3-*anti* diol (*R*,*R*)-**3.96** and allylic alcohol with $POCl_3$.[36] Previous studies have shown pseudo-C_2-symmetric phosphate triene (*R*,*R*)-

3.95 can be desymmetrized via RCM metathesis and the resulting *P*-chiral, non-racemic bicyclic phosphate (*R*,*R*,R_P)-**3.102** can undergo various regio-and chemo-selective reactions.[36] In addition, subtle stereoelectronic properties innate to phosphate tethers further enable the one-pot, sequential RCM/CM/"H_2" protocol to provide streamlined synthesis of advanced polyol synthons. The general protocol for the RCM/CM/"H_2" is shown in Scheme 12.

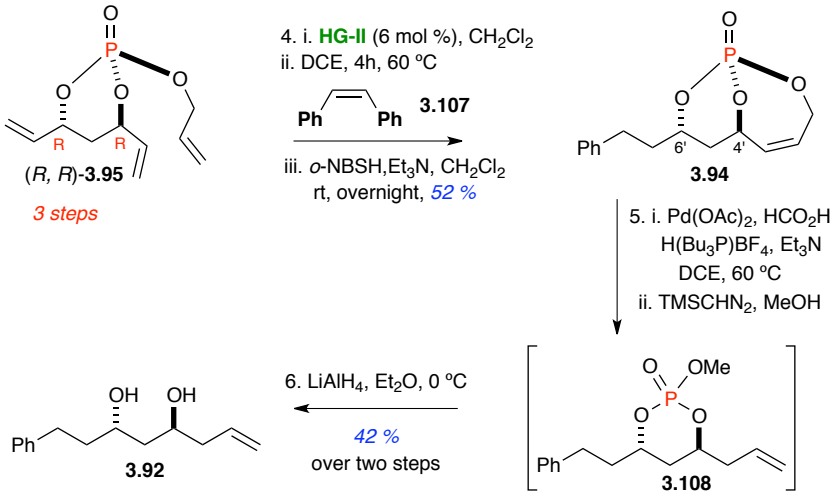
Scheme 12.



Following the previously reported optimized conditions for RCM/CM/H_2,[34] triene (*R*,*R*)-**3.95** was first subjected to RCM reaction with the second-generation Hoveyda–Grubbs (HG-II) catalyst **3.104**[38] (6 mol %) in CH_2Cl_2 (0.007 M) and upon completion of the reaction, solvent was evaporated and CM partner, *cis*-stilbene, in dicholoroethane (DCE) was introduced along with HG–II and refluxing was continued for 6 hours (Scheme 13). It should be noted that CM with styrene was not

productive in comparison to *cis*-stilbene due to deleterious homodimerization of styrene which is a type I olefin partner.[39] Subsequent chemoselective diimide reduction with *o*-NBSH provided the phenyl-substituted phosphate **3.94** in 52% overall yield, representing an 81% average yield for the 3 reactions involved in the one-pot, sequential protocol. Pd-catalyzed, reductive allylic transposition [$Pd(OAc)_2$, $HCOONH_4$] on phosphate **3.108** generated the requisite terminal olefin in excellent regioselectivity, which when followed by tether removal with $LiAlH_4$, provided diol **3.92** as a single diastereomer in 42% overall yield for the two steps.

Scheme 13.

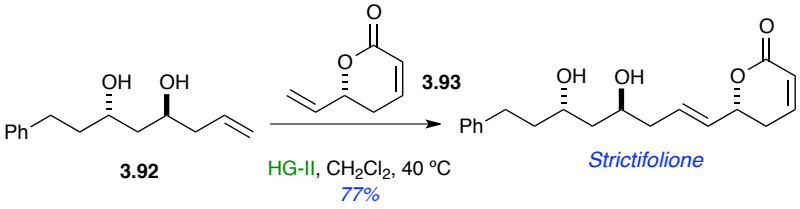


The desired vinyl lactone **3.93** was generated utilizing the Jacobsen HDA methodology[37] and the synthesis was discussed in Chapter 2 (Section 2.2.2.3).

With advanced fragments **3.92** and **3.93** in hand the total synthesis of **3.1** was accomplished via CM of diol alkene **3.92** and vinyl lactone **3.93** in the presence of

HG-II in CH_2Cl_2 to afford **3.1** in 77% yield and excellent *E*-configured olefin selectivity. The spectral data (^1H, ^{13}C, IR, HRMS) and optical rotation of **3.1** were in complete agreement with those reported in the literature.[3]

Scheme 14.

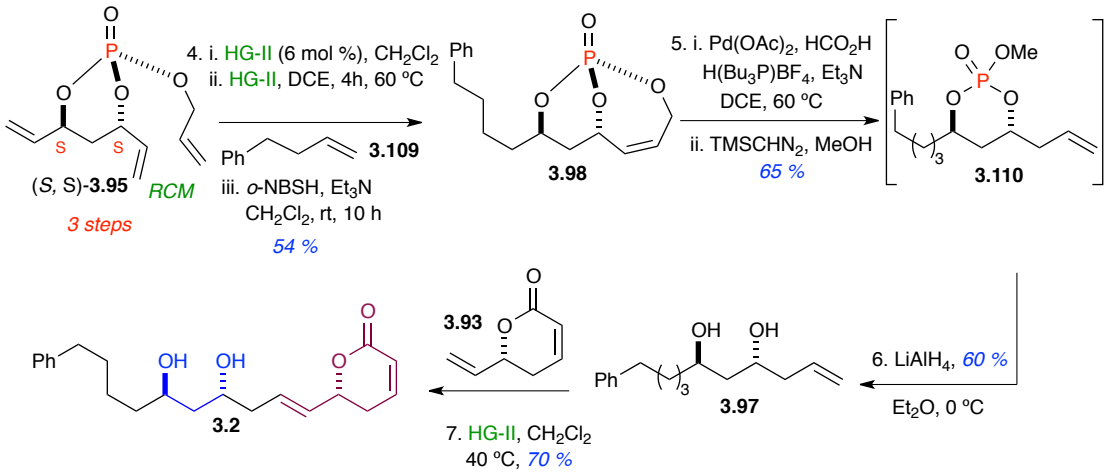


The exploitation of this modular approach to enable chemical library production of analogs of **3.1** is an added advantage. In particular, late-stage CM/RCM/"H_2" (at step 4) and CM at step 7, streamlines this approach. This aspect is further demonstrated in the synthesis of **3.2** starting with the enantiomeric triene (*S*,*S*)-**3.95** and a different CM partner **3.109** as outlined in Scheme 15.

Synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-*2H*-pyran-2-one (**3.2**) is achieved following a similar sequence starting with the enantiomerically pure diene diol (*S*,*S*)-**3.96** (Scheme 16). After completing the RCM reaction with triene (*S*,*S*)-**3.95**, CM was proceeded with the phenyl-but-1-ene (**3.109**) and subsequent hydrogenation generated phosphate **11.7** in 54% overall yield in 3 steps. Pd-catalyzed, reductive allylic transposition afforded monocyclic phosphate **3.110** in 65% yield and tether removal with $LiAlH_4$ provided the key intermediate **3.97** in 60% yield. Cross-metathesis with vinyl lactone **3.93** and **3.97**

furnished the natural product **3.2** in 70% overall yield, and with excellent *E*-olefin selectivity.

Scheme 15

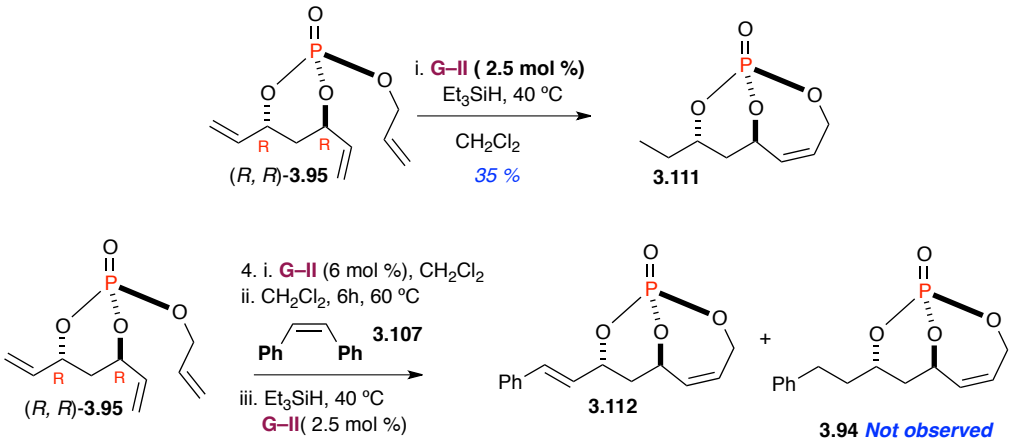


3.3 Future directions and Conclusion

The key advancement of the current route is further development of one-pot procedures, which incorporate all 4 steps in an efficient one-pot, sequential protocol. In this regard, ongoing efforts are focused on the combination of Pd-catalyzed allylic transposition into the one-pot RCM/CM/H_2 sequence. However, reduction with diimide conditions did not facilitate Pd-catalyzed reductive allylic transposition due to excess Et_3N that used in the preceding reaction. A potential solution to this issue is to find a different method for the chemoselective reduction of the exocyclic double bond without encountering additional problems with Ru catalysis, which were used in the previous RCM and CM reactions. Cossy and coworkers reported olefin reductions compatible with Ru catalysis utilizing Et_3SiH/Grubbs–II, and Pt_2O/H_2 in

tandem CM/reduction or RCM/reduction protocols.[40] Initial studies attempted with triene (*R*,*R*)-**3.95**, and RCM followed by reduction with Et_3SiH/ Grubbs–II showed satisfactory results for the chemo-selective reduction of exocyclic double bond. However, application of the same protocol for the RCM/CM product, was not successful and cross metathesis product **3.112** was recovered. In addition Pt_2O/H_2, as well as Lindlar cat:Pd/C(1:2)/H_2, were also tested, but none of them provided satisfactory results. Exploration of new reaction conditions,[41] as well as further development of Et_3SiH-mediated reduction conditions for an alternative to diimide reduction are in order and will be discussed later.

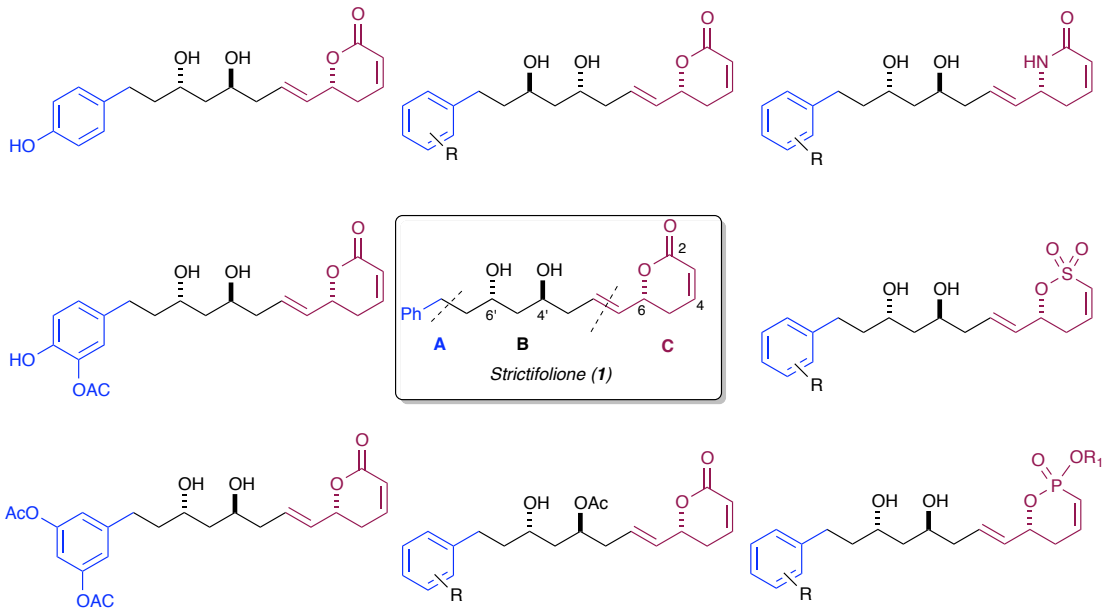
Scheme 16



Another important aspect of the development of new methodologies to facilitate the total synthesis of biologically active natural products is the utilization of such approaches in the synthesis of their simplified analogs. In this regard, various SAR studies related to natural occurring antifungal products highlight the importance of the analog synthesis in searching for new antifungal compounds, which have

shown an improved activities compared to the parent natural products.[42] However, the lack of SAR studies and analog synthesis with respect to natural products **3.1** and **3.2** may be due to the less feasibility of accessing different segments efficiently, according to the known reported synthetic routes. With enhanced interest of these precedents, we have designed the analog synthesis of both **3.1** and **3.2** modifying the substituents in the A, B and C-subunits (Figure 3) via a modular approach, which incorporates a phosphate tether-mediated one-pot, sequential RCM/CM/H_2 protocol. All generated analogues will then be sent for biological screening to our collaborators.

Figure 3: *Proposed library for Strictifolione*



In conclusion, the synthesis of the antifungal agents **3.1** and **3.2** was successfully achieved in 4 linear steps from the starting trienes, (*R*,*R*)-**3.95** and (*S*,*S*)-

3.95, respectively, employing an RCM/CM/"H_2" sequence with simple variation of the CM partners. Of notable importance is the multi-faceted role of the phosphate tether, which avoids the additional use of protecting groups and enables the facile and efficient synthesis for both natural products. Moreover the potential application of aforementioned route in library synthesis of both **3.1** and **3.2** is apparent and will be discussed in the near future.

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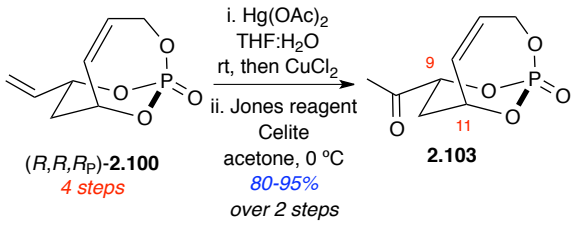
Chapter 4

Experimentals and Spectra for Chapters 2-3

General Experimental Methods

All reactions were carried out in an oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, THF and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3 (Grubbs, R. H.; Rosen. R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). Et_3N was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. ^{31}P NMR spectra was recorded on Bruker DRX-400 spectrometer operating at 162 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

1-((1*S*, 6*R*, 8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanone(2.103)



To a 100 mL round bottom flask under Ar (g) was added mercuric acetate (3.1 g, 9.84 mmol, 2 equiv.) followed by degassed deionized H_2O (12 mL). To this stirring mixture was added via cannula a solution of phosphate (*R, R,* R_P)-**2.100**[1] (1.0 g, 4.92 mmol) in degassed THF (37 mL). The mixture was stirred vigorously until completion (16-24 h, monitored by TLC, 100% EtOAc). A mixture of solid $NaHCO_3$ (0.827 g, 9.8 mmol, 2 equiv.) and $CuCl_2$•$2H_2O$ (1.0 g, 5.9 mmol, 1.2 equiv.) was added and was stirred for 15 minutes. EtOAc (100 mL) was added, the mixture was vigorously stirred, and the layers were separated. The small aqueous layer was extracted with EtOAc (3 x 100 mL) to ensure recovery of the very polar product, and the combined organic layer was washed with $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

To a 250 mL round bottom flask was added crude alcohol (1.086 g), acetone (49 mL, 0.1 M) and Celite® (7.3 g, 1.5 g/mmol). The reaction was cooled to 0 ºC and stirred for 15 min. and Jones reagent (6.28 mL, 16.77 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at 0 ºC until completion (TLC 1:10 Acteone/EtOAc; ~ 2 h) and *i*-PrOH (0.5 mL) was added to consume any leftover Jones reagent, and filtered. The filtrate was concentrated to 15 mL, EtOAc (50 mL) was added and aq. $NaHCO_3$ (4 mL)

was added carefully. The solution was mixed and the layers separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and dry-loaded onto silica. Placement of the substrate impregnated silica on a very short silica gel column and elution with 100% EtOAc (1 column volume) removed any less polar constituents, followed by elution with 1:10 Acetone/EtOAc provided 1.22 g of ketone **2.103** (80% yield) as a while solid.

R_f = 0.3 (100% EtOAc)

M.P: 110–112 ºC;

FTIR (thin film): 2970, 2924, 2893, 2850, 1724, 1615, 1292, 1259, 1091, 1058, 991, 946, 921, 885, 770 cm^{-1};

Optical Rotation: $[\alpha]_D$= -21 (*c* = 0.63, acetone);

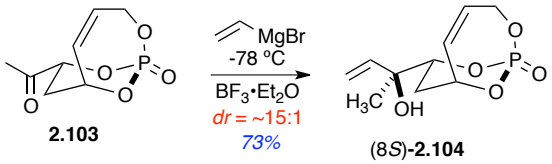
^{1}H NMR (500 MHz, acetone-*d6*) δ (ppm) 6.11 (dddd, *J* = 11.9, 6.5, 3.0, 2.2 Hz, 1H), 5.65 (ddd, *J* = 11.9, 4.0, 2.7 Hz, 1H), 5.31 (dddd, *J* = 24.6, 3.9, 2.1, 1.9 Hz, 1H), 5.05 (dddd, *J* = 14.8, 11.2, 5.0, 2.7 Hz, 1H), 4.97 (dt, *J* = 12.1, 2.3 Hz, 1H), 4.43 (ddd, *J* = 28.3, 14.8, 6.7 Hz, 1H), 2.37 (s, 3H), 2.26 (ddddd, *J* = 14.8, 6.5, 5.2, 3.8, 2.5 Hz, 1H), 2.15 (dddd, *J* = 14.8, 2.6, 2.5, 1.5 Hz, 1H);

^{13}C NMR (125 MHz, acetone-*d6*) δ (ppm) 205.8 (d, J_{CP} = 12.0 Hz), 129.3, 128.7, 79.6 (d, J_{CP} = 7.2 Hz), 77.4 (d, J_{CP} = 7.1 Hz), 63.5 (d, J_{CP} = 6.4 Hz), 31.3 (d, J_{CP} = 6.0 Hz), 26.2;

^{31}P NMR (162 MHz, acetone-*d6*) δ (ppm) -3.64;

HRMS cald for $C_8H_{11}NaO_5P$ $(M+Na)^+$ 241.0242; found 241.0235 (TOF MS ES+).

(*R*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-ol:(2.104)



A 15 mL flask containing ketone **2.103** (10 mg, 0.05 mmol) was added Na dried THF (0.5 mL, 0.1 M), BF_3•OEt_2 (5.8 µL, 0.05 mmol) and stirred for 15 min. and it was cooled to -82 ºC (dry Ice and EtOAc). Freshly prepared vinyl magnesium bromide (0.28 mL, 1.0 M in THF, 3 equiv.) was added slowly along the side of the flask. The reaction mixture was stirred at -82 ºC for 1.5 h (monitored by TLC analysis 3:1 CH_2Cl_2/Acetone) and reaction was cannulated in to 10 % HCl (1 mL) at 0 ºC. The reaction mixture was extracted with EtOAc (3 x 4 mL) and the organic layers collected. The combined organic layers were then washed with 20 mL brine, dried with Na_2SO_4. Purification by flash chromatography with a gradient 5:1 CH_2Cl_2/Acetone to 3:1 CH_2Cl_2/Acetone afforded tertiary alcohol (8*S*)**-2.104** (7.4 mg, 73 % yield) as a white crystalline solid.

R_f = 0.3 (3:1 CH_2Cl_2/Acetone) ;

M.P: 118–121 ºC;

FTIR (thin film): 3406, 2981, 2935, 1610, 1263, 1224, 1161, 1072, 1031, 983, 921, 883, 771 cm^{-1};

Optical Rotation: $[\alpha]_D$ = -68.6 (*c* = 3.45, CH_2Cl_2);

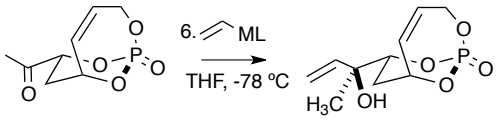
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.04 (dddd, *J* = 11.9, 6.7, 3.1, 2.2 Hz, 1H), 5.80 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.58 (ddd, *J* = 11.9, 3.9, 2.7 Hz, 1H), 5.39 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.23 (m, 1H), 5.21 (dd, *J* = 10.9, 1.2 Hz, 1H), 5.00 (dddd, *J* = 14.7, 5.6, 5.6, 2.7 Hz, 1H), 4.39 (dddd, *J* = 18.6, 16.8, 12.0, 6.7 Hz, 2H), 2.37 (ddd, *J* = 14.9, 12.2, 6.4 Hz, 1H), 2.24 (br s, 1H), 1.75 (ddd, *J* = 14.8, 3.6, 2 Hz, 1H), 1.38 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 139.2, 129.9, 127.9, 115.5, 81.4 (d, J_{CP} = 7.2 Hz), 77.2 (d, J_{CP} = 6.6 Hz), 73.9 (d, J_{CP} = 9.1 Hz), 63.2 (d, J_{CP} = 6.4 Hz), 29.1 (d, J_{CP} = 5.5 Hz), 24.4;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.9;

HRMS cald for $C_{10}H_{15}NaO_5P$ $(M+Na)^+$ 269.0555; found 269.0532 (TOF MS ES+).

Procedure B



ML= $YbCl_2$, dr = ~ 50:1 70%
ML= $CeCl_2$, dr = ~ 1.5:1 87 %

Lithium chloride (15.5 mg, 0.4 mmol) and anhydrous cerium (III) trichloride (23 mg, 0.2 mmol) were measured in to a round-bottomed flask and dried under vaccum at 60 ºC for 2 hours, 80 ºC for 2 h and 150 ºC for 8 h. To the dried salt mixture, Na dried THF (0.1 mL) was added under argon atmosphere and stirred vigorously for 2.5 h at RT, producing a near colorless solution and then cooled to -78 ºC. To this solution freshly prepared vinyl magnesium bromide (0.2 mL, 0.2 mmol, 1 M in THF) was added and

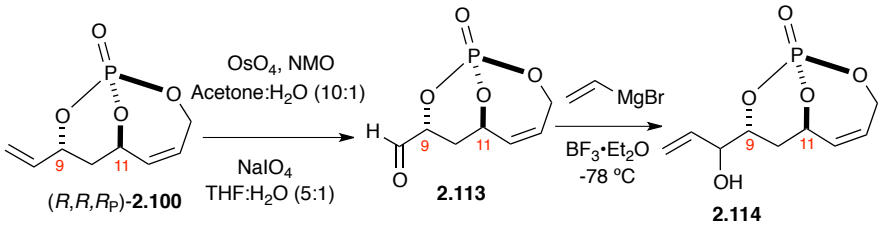
stirred for 1 h at -78 ºC. This yellowish tan color solution was then added to ketone **2.103** (10 mg, 0.05 mmol) in THF (0.5 mL) by cannula with a THF (0.1 mL) rinse. The reaction mixture was stirred for 1–1.5 h at -78 ºC until all the starting materials were consumed (monitored by TLC 3:1 CH_2Cl_2/Acetone). The solution was cannulated back to 10 % HCl (0.5 mL) solution at 0 ºC and vigorously stirred for 15 min. After the solution had warmed to rt, the layers were separated. The aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were washed sequentially with brine (3 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography with a gradient 5:1 CH_2Cl_2/Acetone to 3:1 CH_2Cl_2/Acetone provided 2:1 mixture of **2.104** ((8*S*)-**2.104**: (8*R*)-**2.104** = 2:1) (10 mg, 87% yield) as a crystalline white solid. [Note: Both (8*S*)-**2.104** and (8*R*)-**2.104** have same R_f value for all most all the solvent gradients attempted.]

Procedure C

The commercially available $YbCl_3 \bullet 6H_2O$ (76 mg, 0.28 mmol) was dried in vacuo at 140 ºC for 2 h. To the dried salt, 0.4 mL of Na dried THF was added under Ar atmosphere, and the mixture was sonicated for 0.5 h using an ultrasonic cleaner. The obtained suspension was cooled at -78 ºC, and freshly prepared vinyl magnesium bromide (0.2 mL, 0.18 mmol, 1 M in THF) was added and stirred at same temperature for 30 min. The ketone **2.103** (10 mg, in THF (0.5 mL) was cannulated to this solution slowly and rinsed with THF (0.2 mL). The mixture was stirred at -78 ºC for 1-1.5 h until all the starting materials were consumed by TLC analysis (3:1 CH_2Cl_2/Acetone) and quenched with 1 M aqueous HCl via back cannulation of the reaction mixture to the 1 M

HCl solution (0.5 mL) at 0 ºC. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 2 mL) and combined organic layers were dired over $NaSO_4$. Purification by flash chromatography with a gradient 5:1 CH_2Cl_2/Acetone to 3:1 CH_2Cl_2/Acetone provided (8*S*)-**2.104** (8 mg, 70%) as a crystalline white solid.

(1*S*,6*R*,8*R*)-8-(1-hydroxyallyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (2.114)



To a stirred solution of **2.100** (100 mg, 0.5 mmol) in acetone (4.5 mL) and H_2O (0.5 mL) at 12 ºC, was added OsO_4 (2.5 mg, 0.01 mmol) followed NMO (75 mg, 0.6 mmol). The reaction mixture was stirred for 6–8 h until all the starting materials were consumed (monitored by TLC 10:1 EtOAc/Acetone). Solid Na_2SO_3 (~20 mg) was then added and the reaction mixture was left to stir at RT for further 1 h. The mixture was then filtered through Celite® and concentrated under reduced pressure. This crude diol was subjected to next reaction with out further purification.

The solution of the preceding diol (78 mg, 0.33 mmol) in THF (23 mL) and pH 7 buffer (4.5 mL) was treated with $NaIO_4$ (424 mg, 1.98 mmol) in one portion. The resulting mixture was stirred for 2 h until all the starting materials were consumed (monitored by TLC, 10:1 EtOAc/Acetone). The mixture was then filtered through Celite® and resulting solution was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. Simple passage of the crude reaction mixture through a short silica plug (100 % EtOAc) afforded aldehyde **2.113** as a colorless oil and immediately used in next reaction.

To a stirring solution of aldehyde **2.113** (25 mg, 0.12 mmol) in Na dried THF (1.2 mL, 0.1 M) and BF_3•OEt_2 (15.5 μL, 0.12 mmol) at -78 ºC, was added freshly prepared vinyl magnesium bromide (0.5 mL, 1.0M in THF, 4 equiv.) slowly along the side of the flask. The reaction mixture was stirred at the same temperature ºC for 2 h (monitored by TLC analysis 3:1 CH_2Cl_2/Acetone) and reaction was cannulated in to 10 % HCl (1 mL) at 0 ºC. The reaction mixture was extracted with EtOAc (3 x 4 mL) and the organic layers collected. The combined organic layers were then washed with 20 mL brine, dried with Na_2SO_4. Purification by flash chromatography with a gradient 5:1 CH_2Cl_2/Acetone to 3:1 CH_2Cl_2/Acetone afforded desired secondary alcohol (8*S*)-**2.114** (2.6 mg, 20 % un-optimized yield) as yellow oil.

R_f = 0.25 (3:1 CH_2Cl_2/Acetone) ;

FTIR (thin film): 3406, 2981, 2935, 1615, 1263, 1224, 1161, 1072, 1031, 983, 921, 883, 771 cm^{-1};

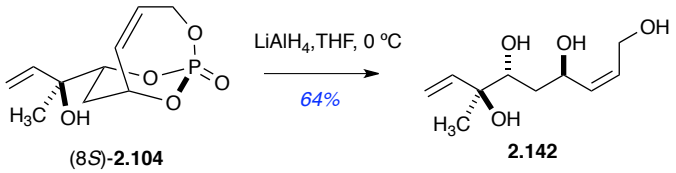
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.01–5.93 (m, 1H), 5.75 (ddd, *J* = 17.1, 10.7, 5.5 Hz, 1H), 5.53 (ddd, *J* = 11.9, 6.7, 2.9 Hz, 1H), 5.36 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.25 (ddd, *J* = 10.5, 5.5, 1.2 Hz 1H), 5.24 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.98 (ddt, *J* = 14.3, 5.6, 2.7 Hz, 1H), 4.50 (ddt, *J* = 12.1, 3.5, 1.6 Hz, 1H), 4.38–4.26 (m, 2H) 2.36–2.27 (m, 1H), 1.67 (dd, *J* = 11.8,10.8 Hz, 1H), 1.2 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 134.2, 129.9, 127.9, 118.3, 78.8 (d, J_{CP} = 6.8 Hz), 77.2 (d, J_{CP} = 11.3 Hz), 73.6 (d, J_{CP} = 10.1 Hz), 73.6 (d, J_{CP} = 10.1 Hz), 28.7 (d, J_{CP} = 5.7 Hz);

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -3.26 (t, J_{PH} = 23.3 Hz);

HRMS cald for $C_9H_{13}NaO_5P$ $(M+Na)^+$ 255.0398; found 255.0403 (TOF MS ES+).

(4*R*,6*R*,7*R*,*Z*)-7-methylnona-2,8-diene-1,4,6,7-tetraol (2.142)



(8*S*)-**2.104** **2.142**

To the phosphate (8*S*)-**2.104** (66 mg, 0.268 mmol) was added 4.0 mL of THF (0. 02 M) under argon atmosphere and cooled to 0 ºC. Then $LiAlH_4$ was slowly added (31 mg, 0.0.815 mmol, 3 equiv.) to the reaction mixture and the reaction was stirred at 0 ºC for 1 h until all starting materials were consumed (monitored by TLC 1:1 EtOAc: acetone) and allowed to continue for 15 more minutes at 0 ºC. (total reaction time typically about 1 h). The reaction was quenched by slow, dropwise addition of 31 μL of H_2O, followed by slow, dropwise addition of 30 μL of 15 % NaOH (aq), and finishing with an addition of 93 μL of H_2O. At this point, the mixture is allowed to reach room temperature until all salts appear to become a white color. SiO_2 was then added and the solvent removed, and was placed on a short silica gel plug and eluted with a 1:1 EtOAc: acetone mixture, producing 35 mg (64% yield) of tetraol **2.142**.

R_f = 0.3 (1:1 EtOAc/Acetone);

Optical Rotation: $[\alpha]_D$ = +46 (*c* = 0.05, acetone);

FTIR (thin film): 3339, 2951, 2910, 2877, 1458, 1410, 1238, 1099 cm-1;

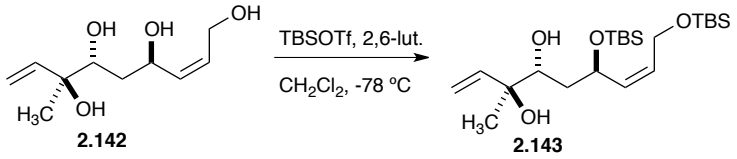
^{1}H NMR (500 MHz, acetone-*d6*) δ (ppm) 5.96 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.50 (m, 2H), 5.28 (dd, *J* = 17.4, 2.1 Hz, 1H), 5.02 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.68 (dddd, *J* = 6.6, 4.6, 2.6, 2.3 Hz, 1H), 4.19 (ddd, *J* = 12.4, 5.4, 1.7 Hz, 1H), 4.10 (ddd, *J* = 12.6, 4.2, 3.8 Hz,

1H), 3.91 (d, J = 4.8 Hz, 1H), 3.70 (m, 3H), 3.54 (s, 1H), 1.67 (ddd, J = 15.0, 9.3, 1.9 Hz, 1H), 1.44 (ddd, J = 15.0, 7.8, 2.6 Hz, 1H), 1.22 (s, 3H);

^{13}C NMR (126 MHz, acetone-*d6*) δ ppm 144.2, 135.9, 130.4, 112.7, 75.6, 74.6, 65.4, 58.7, 40.3, 24.6;

HRMS cald for $C_{10}H_{18}NaO_4$ $(M+Na)^+$ 225.1103; found 225.1105 (TOF MS ES+).

(3*S*,4*R*,6*R*,*Z*)-6,9-bis((*tert*-butyldimethylsilyl)oxy)-3-methylnona-1,7-diene-3,4-diol (2.143)



To the solution of tetraol **2.142** (17 mg, 0.08 mmol) in 1 mL of CH_2Cl_2 (0.1M) was added 2,6-lutidine (41 μL, 0.36 mmol, 4.5 equiv.). The solution was then cooled to -78 ºC and TBSOTf (40 μL, 0.17 mmol, 2.2 equiv.) was added dropwise to the solution with stirring. The reaction was stirred at -78 ºC for 2 h, until all the starting materials were consumed, monitored by TLC (4:1 Hexane/EtOAc). The reaction was diluted with 2 mL of CH_2Cl_2 and quenched with 1 mL of saturated aqueous NH_4Cl, and layers were separated, and the aqueous layer was extracted 3 more times with CH_2Cl_2. The combined organic layers were then washed with brine, dried with $MgSO_4$. Purification by flash chromatography (hexane: ethyl acetate) provided bis-TBS protected diol **2.143 (**25 mg, 75 % yield) as a yellow oil.

R_f = 0.3 (4:1 Hexane/EtOAc)

Optical Rotation: $[\alpha]_D$ = +18 (*c* = 0.25, CH_2Cl_2);

FTIR (thin film): 3459, 3010, 2954, 2879, 2858, 1079, 1009, 923 cm-1;

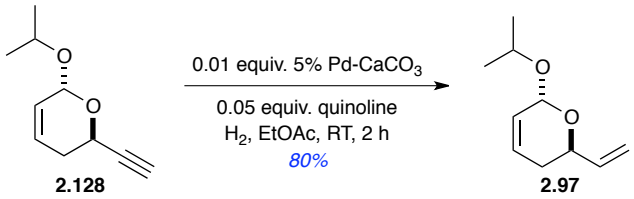
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.82 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.63–5.49 (m, 2H), 5.29 (dd, *J* = 17.4, 1.6 Hz, 1H), 5.12 (dd, *J* = 10.9, 1.6 Hz, 1H), 4.83 (dt, *J* = 8.3, 4.3, Hz, 1H), 4.21 (ddd, *J* = 12.9, 6.5, 1.3 Hz, 1H), 4.13 (ddd, *J* = 13.4, 5.2, 1.7 Hz, 1H),

3.78 (m, 1H), 3.71 (d, J = 2.9 Hz, 1H), 2.49(s, 1H), 1.64 (t, J = 4.3 Hz, 2H), 1.27(s, 3H), 0.9 (s, 18H), 0.5 (s, 12H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 140.8, 133.5, 128.8, 113.7, 74.9, 74.3, 68.1, 59.4, 38.5, 25.9 (2C), 25.8 (2C), 25.7 (2C), 24.6, 18.3, 18.0, -4.5, -5.2, -5.3(2);

HRMS cald for $C_{22}H_{46}NaO_4Si_2$ $(M+Na)^+$ 453.2832; found 453.2811 (TOF MS ES+).

(2*R*,6*R*)-6-isopropoxy-2-vinyl-3,6-dihydro-2*H*-pyran (2.97)



To a 100 mL round bottom flask was added alkyne **2.128**[2] (1.10 g, 6.53 mmol) freshly distilled quinoline (42 mg, 0.327 mmol, 0.05 equiv.), and degassed EtOAc (65 mL, 0.1M) and was placed under a H_2 atmosphere. To this stirring mixture was added 5% Pd-$CaCO_3$ (139 mg, 0.065 mmol Pd, 0.01 equiv.). The reaction was allowed to proceed for 2 h (monitored by GC and TLC 20:1 Hexane/Et_2O) and the mixture was filtered through Celite® and the solvent removed *gently*. The crude product was passed through a short SiO_2 plug (20:1 petroleum ether/ Et_2O) to provide desired alkene **2.97** (877 mg 80% yield) as clear oil.

R_f = 0.35 (20:1 Hexane/Ether)

Optical Rotation: $[\alpha]_D$ = +59 (*c* = 0.37, CH_2Cl_2)

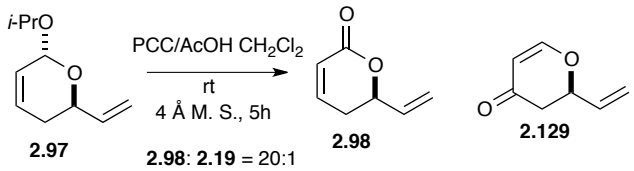
FTIR: (neat) 3080, 3045, 2970, 2924, 2894, 1647, 1458, 14231182, 1126, 1101, 1034, 1009, 860, 719, 783 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.04–5.99 (m, 1H), 5.91 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.73 (ddd, *J* = 10.0, 2.8, 1.5 Hz, 1H), 5.30 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.16 (dt, *J* = 10.6, 1.6 Hz, 1H), 5.12 (d, *J* = 1.2 Hz, 1H), 4.43 (ddt, *J* = 10.0, 4.8, 0.6 Hz, 1H), 4.01 (q, *J* = 6.3 Hz, 1H), 2.15–2.01 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 138.2, 128.4, 126.1, 115.4, 93.2, 69.6, 66.7, 30.2, 23.8, 22.1;

HRMS cald. for $C_{10}H_{16}NaO_2$ $(M+Na)^+$ 191.1048; found 191.1052 (TOF MS ES+).

(*R*)-6-vinyl-5, 6-dihydro-2*H*-pyran-2-one (2.98)



A solution of lactol **2.97** (1.01 g, 5.99 mmol) in CH_2Cl_2 (120 mL, 0.05M) was treated with PCC (6.5 g, 29.95 mmol), 4 Å molecular sieves (1.14 g, 190 mg/mmol of **2.97**) and AcOH (3.6 g, 59.9 mmol). After stirring at RT for 5 h, water (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 100 mL) and the solvent was removed *gently*. The crude product was passed through a short SiO_2 plug, eluting with 5:1 Hexane/EtOAc to provide desired lactone **2.98** (596 mg 82% yield) as yellow oil.

R_f = 0.18 (5:1 Hexane/EtOAc);

Optical Rotation: $[\alpha]_D$ = +168 (*c* = 0.525, $CHCl_3$);

FTIR: (neat) 3080, 3045, 2970, 2924, 2894, 1722, 1647, 1423, 1381, 1246, 1126, 1101, 860, 719, 783 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.89 (ddd, *J* = 9.8, 5.4, 3.1 Hz, 1H), 6.06 (ddd, *J* = 9.8, 2.4, 1.3 Hz, 1H), 5.96 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H), 5.39–5.43 (ddd, *J* = 17.2, 1.3, 1.0 Hz, 1H), 5.31–5.29 (ddd, *J* = 10.6, 1.1, 1.1 Hz, 1H)), 4.96–4.91 (m, 1H), 2.53–2.40 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 163.8, 144.4, 134.8, 121.6, 117.9, 77.8, 29.4;

HRMS cald. for $C_7H_8NaO_2$ $(M+Na)^+$ 124.0524; found 124.0519 (TOF MS ES+).

(*R*)-2-vinyl-2*H*-pyran-4(3*H*)-one (2.129).

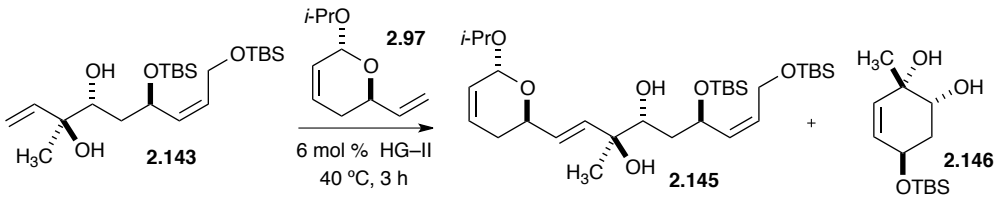
$\mathbf{R_f}$ = 0.21 (5:1 Hexane/EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37 (d, *J* = 6.0 Hz, 1H), 5.96 (ddt, *J* = 13.4, 10.7, 6.7 Hz, 1H), 5.45–5.37 (m, 2H), 5.32 (d, *J* = 5.8, 4.8 Hz, 1H)), 4.94–4.87 (m, 1H), 2.66–2.51 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 191.8, 162.7, 134.3, 118.3, 107.2, 79.4, 41.4;

HRMS cald. for $C_7H_8NaO_2$ $(M+Na)^+$ 124.0524; found 124.0526 (TOF MS ES+).

(1*R*,2*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylcyclohex-3-ene-1,2-diol (2.146)



To a 25 mL pressure tube under argon was added diol **2.143** (10 mg, 0.023 mmol), ^{i}Pr protected lacto1 **2.97** (12 mg, 0.07 mmol) and degassed CH_2Cl_2 (0.23 μL, 0.1 M). To this reaction mixture was added HG–II catalyst (1 mg, 0.0013 mmol, 6 mol %) and refluxed for 3 h. The reaction was cooled to rt, and solvent was removed under reduced pressure. Purification by flash chromatography (4:1 Hexane:EtOAc) was afforded the both **2.146** (3.3 mg, 68% yield) and **2.145** (1.8 mg 12% yield) as yellow color oil.

R_f = 0.2 (4:1 Hexane/EtOAc) for **2.146** and **R_f** = 0.3 (4:1 Hexane/EtOAc) for **2.145**;

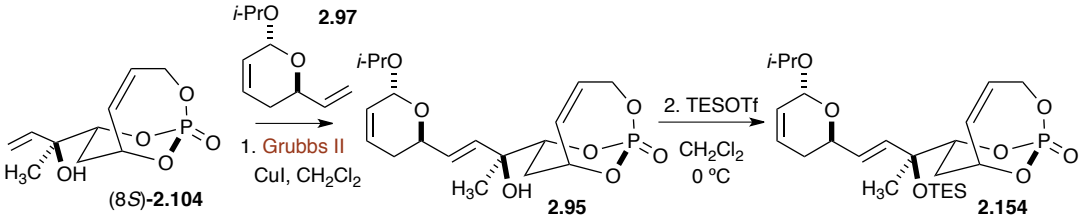
FTIR (thin film): 3400, 3010, 2954, 2925, 2854, 2488, 1610, 1461, 1361, 1060 cm-1;

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.73 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.61–5.57 (m, 1H), 4.43 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.89 (ddd, *J* = 8.0, 5.4, 2.6 Hz, 1H), 2.26 (d, *J* = 5.6 Hz, 1H), 2.08 (ddd, *J* = 13.2, 8.0, 4.9 Hz, 1H), 2.03 (s, 1H), 1.81 (ddd, *J* = 13.4, 5.9, 2.8 Hz, 1H), 1.36 (s, 3H), 0.90 (d, J = 2.9 Hz, 9H), 0.09 (d, J = 2.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 132.4, 131.7, 71.8, 69.6, 65.0, 36.9, 26.6, 25.8(3C), 18.2, -4.6, -4.7;

HRMS cald for $C_{13}H_{26}NaO_3Si$ $(M+Na)^+$ 281.1549; found 281.1541 (TOF MS ES+).

(1*S*,6*R*,8*R*)-8-((*S*,*E*)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-2-((triethylsilyl)oxy)but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.154)



To a 25 ml pressure tube under argon was added phosphate (8*S*)-**2.104** (29 mg, 0.12 mmol, 1 equiv.), ^{i}Pr protected lacto1 **2.97** (60 mg, 0.35 mmol) and degassed CH_2Cl_2 (0.5 mL, 0.25M). To this reaction mixture was added Grubbs–II catalyst (7 mg, 0.008 mmol, 10 mol %) and dried CuI (3.4 mg, 0.02 mmol, 15 mol %) and refluxed for 6h–10h until almost all the starting materials were consumed. (Monitored by TLC analysis 6:1 $CHCl_3$/MeOH). The reaction was cooled to rt, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to TES protection with out further purification. [Note: Separation of the cross-metathesis product **2.95** and the unreacted phosphate (8*S*)-**2.104** was very difficult and could be easily obtained after TES protection of the crude product].

To the crude product mixture in CH_2Cl_2 was added freshly distilled 2,6 lutidine (19 μL, 0.13 mmol) and reaction was cooled to 0 ºC. To the stirring reaction mixture was added TESOTf (29 μL, 0.13 mmol) and reaction was stirred for 2 h at 0 ºC until all the starting materials were consumed. (TLC 8:1 CH_2Cl_2/EtOAc). Reaction was quenched with NH_4Cl and layers were separated. Aqueous layer was extracted CH_2Cl_2 (3 x 2 mL) and combined organic layers were dried with $MgSO_4$ and concentrated under reduced

pressure. Purification by flash chromatography (8:1 CH_2Cl_2/EtOAc) provided the TES protected product **2.154** (22 mg) in 40% overall yield .

R_f = 0.2 (8:1 CH_2Cl_2/EtOAc) for TES protected product **2.154**;

= 0.3 (8:1 CH_2Cl_2/EtOAc) for TES protected starting material **2.153**;

FTIR (thin film): 3383, 3038, 2955, 2935, 2876, 1610, 1375, 1299, 1180, 1088, 997, 981 cm-1;

Optical Rotation: $[\alpha]_D$ = -7.4 (*c* = 0.54, $CHCl_3$);

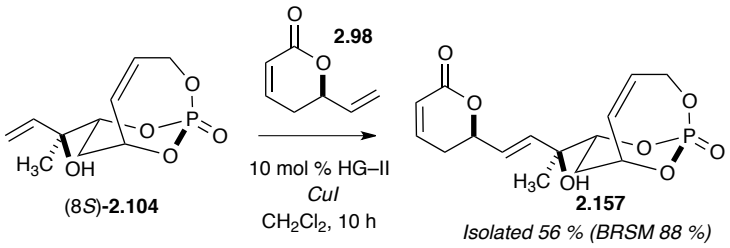
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.04–5.98 (m, 2H), 5.8 (dd, *J* = 15.7, 6.1 Hz, 1H), 5.7 (dtd, *J* = 11.5, 2.8, 1.5 Hz, 1H), 5.7 (dd, *J* = 15.9, 0.9 Hz, 1H), 5.5 (ddd, *J* = 11.8, 3.9, 2.5 Hz, 1H), 5.2 (bd, *J* = 26.4 Hz, 1H), 5.1 (dd, *J* = 1.3 Hz, 1H), 5.0 (dtd, *J* = 14.6, 5.6, 2.7 Hz, 1H), 4.4 (ddd, *J* = 10.2, 5.9, 3.8 Hz, 1H), 4.4 (ddd, *J* = 27.7, 14.7, 6.7 Hz, 1H), 4.2 (dt, *J* = 11.9, 1.6 Hz, 1H), 4.0 (q, *J* = 6.2 Hz, 1H), 2.3 (ddd, *J* = 14.7, 12.0, 6.3 Hz, 1H), 2.1–2.0 (m, 2H), 1.8 (ddd, *J* = 15.2, 3.4, 2.1 Hz, 1H), 1.4 (s, 3H), 1.2 (d, *J* = 6.2 Hz, 3H), 1.2 (d, *J* = 6.2 Hz, 3H), 1.0 (dd, *J* = 8.0 Hz, 9H), 0.6 (dq, *J* = 8.2, 2.3 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 134.8, 131.2, 130.0, 128.4, 127.8, 126.1, 93.4, 81.3(d, J_{CP} = 7.4 Hz), 77.2 (d, J_{CP} = 7.0 Hz), 75.5 (d, J_{CP} = 10.2 Hz), 70.0, 66.4, 63.0 (d, J_{CP} = 6.3 Hz), 30.7, 29.0 (d, J_{CP} = 5.3 Hz), 23.8, 22.5, 22.3, 7.1(3C), 6.6 (3C);

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.88 (t, J_{PH} = 23.4 Hz);

HRMS cald for $C_{24}H_{41}O_7PSiNa$ $(M+Na)^+$ 523.2257; found 523.2253 (TOF MS ES+).

(*R*)-6-((*S*,*E*)-3-hydroxy-3-((1*S*,6*R*,8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (2.157)



To a 25 mL flask under argon was added phosphate (8*S*)-**2.104** (191 mg, 0.775 mmol, 1 equiv.), lactone **2.98** (48 mg, 0.388 mmol, 0.5 eq) and degassed CH_2Cl_2 (3.2 mL, 0.25M with respect to phosphate (8*S*)-**2.104**). To this reaction mixture was added HG–II catalyst (14.5 mg, 0.023 mmol, 4 mol %) and dried CuI (11 mg, 0.058, 15 mol %) and refluxed for 3 h. Another 0.3 eq of lactone (28 mg, 0.232 mmol) in 0.5 mL of CH_2Cl_2 and HG–II (3.6 mg, 0.0058 mmol, 2.5 mol%) was added and refluxing was continued for 2 h. Similarly, lactone (28 mg. 0.232 mmol, 0.3 eq) and HG–II (3.6 mg, 0.0058 mmol, 2.5 mol%) was added to the reaction mixture after 2 h of refluxing once more and reaction was refluxed at the same temperature for another 3 h [total reaction time was 10 h]. (Portionwise addition of lactone prevent the homo-dimerization of lactone) The reaction was cooled to RT, and the solvent was removed under reduced pressure. Purification by flash chromatography (1:6 Hexane:EtOAc to 100 % EtOAc) provided **2.157** (155 mg, 58 % isolated yield and 88 % BRSM) color less oil.

$\mathbf{R_f}$ = 0.2 (10:1 EtOAc/Acetone);

FTIR (thin film): 3411, 3380, 3101, 2955, 2922, 2853, 2359, 2341, 1717, 1383, 1292, 1258, 1072, 1036, 993 cm-1;

Optical Rotation: $[\alpha]_D$ = -18.0(*c* = 0.165, $CHCl_3$);

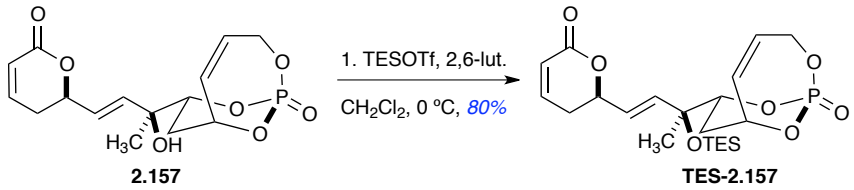
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.91 (ddd, *J* = 9.5, 5.3, 3.1 Hz, 1H), 6.08 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.04(dd, *J* = 1.1, 2.5 Hz, 1H), 6.01 (dd, *J* = 15.5, 5.6 Hz, 1H), 5.80 (dd, *J* = 15.5, 1.3 Hz, 1H), 5.60 (ddd, *J* = 11.9, 3.8, 2.5 Hz, 1H), 5.23 (d, *J* = 24.9 Hz, 1H), 5.06–4.93 (m, 2H), 4.45–4.34 (m, 2H), 2.55–2.31 (m, 2H), 1.75 (d, *J* = 14.9 1H), 1.65 (br s, 1H) 1.44–1.35 (m, 3H), 1.30–1.21 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 163.8, 144.8, 134.3, 129.9, 127.9, 127.5, 121.5, 80.9 (d, J_{CP} = 7.2 Hz), 77.1 (d, J_{CP} = 19.4 Hz), 77.2 (d, J_{CP} = 6.6 Hz), 73.5 (d, J_{CP} = 9.3 Hz), 63.2 (d, J_{CP} = 6.3 Hz), 29.8, 29.2 (d, J_{CP} = 5.5 Hz), 24.9;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.92 (t, J_{PH} = 26.7 Hz);

HRMS cald for $C_{15}H_{19}NaO_7P$ $(M+Na)^+$ 365.0776; found 365.0771 (TOF MS ES+).

(*R*)-6-((*S*,*E*)-3-((1*S*,6*R*,8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-3-((triethylsilyl)oxy)but-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (TES-2.157).



2.157 **TES-2.157**

To the solution of phosphate **2.157** (52 mg, 0.152 mmol) in 1.5 mL of CH_2Cl_2 (0.1M) was added 2,6-lutidine (70.6μL, mmol, 4.0 equiv.). The solution was then cooled to 0 ºC and TESOTf (69.0 μL, mmol, 2.0 equiv.) was added dropwise to the solution with stirring. The solution was stirred at 0 ºC for 3h, until all the starting materials were consumed, monitored by TLC (100 % EtOAc). The reaction was diluted with 2 mL of CH_2Cl_2 and quenched with 1 mL of saturated aqueous NH_4Cl, and layers were separated, and the aqueous layer was extracted 3 more times with CH_2Cl_2. The combined organic layers were then washed with brine and dried with $MgSO_4$. Purification by flash chromatography (1:3 hexane: ethyl acetate) provided 54.6 mg of the silyl protected phosphate **TES-2.157** as a yellow oil in 80 % yield.

R_f = 0.5 (100 % EtOAc);

FTIR (thin film): 3033, 2953, 2912, 2876, 2359, 2332, 1724, 1618, 1458, 1380, 1302, 1244, 1090, 1060, 980 cm-1;

Optical Rotation: $[\alpha]_D$ = -2.9(*c* = 2.25, $CHCl_3$);

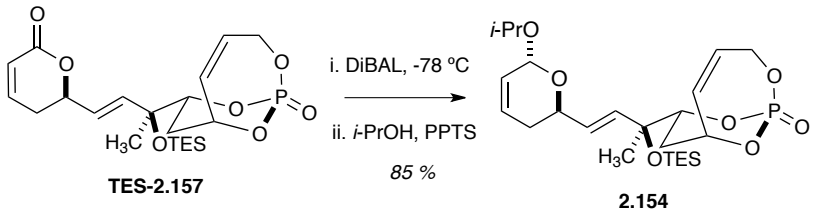
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.90 (ddd, J = 9.5, 5.3, 3.1 Hz, 1H), 6.07 (d, J = 9.8 Hz, 1H), 6.04–5.99 (m, 1H), 5.92–5.77 (m, 2H), 5.58 (ddd, J = 11.8, 3.5, 2.7 Hz, 1H), 5.22 (d, J = 24.5 Hz, 1H), 5.03–4.92 (m, 2H), 4.35 (ddd, J = 27.8, 14.8, 6.7 Hz, 1H), 4.25 (td, J = 11.9, 1.7 Hz, 1H), 2.51–2.36 (m, 2H), 2.29 (ddd, J = 14.7, 12.1, 6.3 Hz, 1H), 1.80 (d, J = 14.7 Hz, 1H), 1.42 (s, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.62 (qd, J = 8.2, 2.0 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 156.8, 137.6, 130.5, 123.0, 120.8 (2C), 114.6, 73.8 (d, J_{CP} = 7.3 Hz), 70.1, 70.2, 68.6 (d, J_{CP} = 10.2 Hz), 56.0 (d, J_{CP} = 6.4 Hz), 22.9, 21.9 (d, J_{CP} = 5.3 Hz), 15.5, 0.1 (3C), -0.4 (3C);

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -3.03 (t, J_{PH} = 23.9 Hz)

HRMS cald for $C_{21}H_{33}NaO_7PSi$ $(M+Na)^+$ 479.1631; found 479.1604 (TOF MS ES+).

(1*S*,6*R*,8*R*)-8-((*S*,*E*)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-2-((triethylsilyl)oxy)but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene1-oxide (2.154)

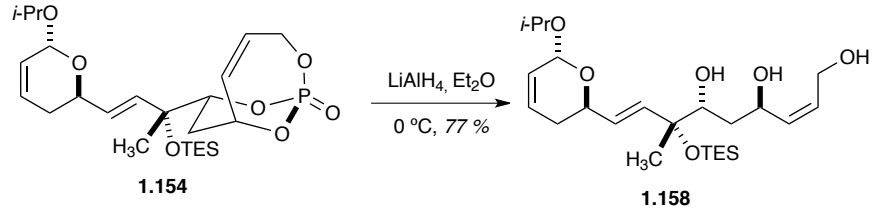


TES-2.157 **2.154**

A solution of **TES-2-157** (48 mg, 0.105 mmol) in 1.3 mL of CH_2Cl_2 was treated with 0.16 mL of DIBAL–H (1.0 M in toluene) at –78 ºC. Reaction was removed from –78 ºC and kept at -30 ºC temperature for 10 min and slowly warmed to 0 ºC. After 1 h, total consumption of starting material by TLC (1:1 CH_2Cl_2/EtOAc) was observed and 1 mL of saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL) and dried with Na_2SO_4, and concentrated and oily product obtained was directly used in the next step without further purification. The product was dissolved in 0.5 mL of anhydrous benzene and 0.26 mL of *i*-PrOH and catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)(1.3 mg, 5 mol %) was added. The reaction mixture was stirred at 25 ºC for 2 h and quenched by addition of 1 mL of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4. Purification with flash chromatography (1:4 Hexane/EtOAc) afforded **2.154** as a colorless oil in 85 % overall yield for two steps.

R_f = 0.5 (1:4 Hexane/EtOAc); [Note**:** Spectral data are provided in page X]

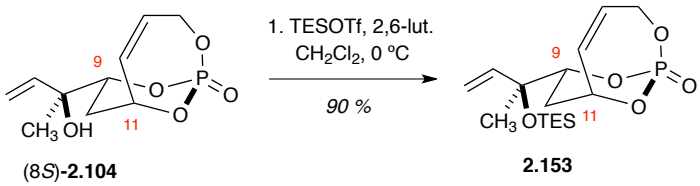
(2*Z*,4*R*,6*R*,7*R*,8*E*)-9-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-7-methyl-7-((triethylsilyl)oxy)nona-2,8-diene-1,4,6-triol (2.158)



1.154 **1.158**

To the phosphate **2.154** (49.3 mg, 0.099 mmol) was added 3.52 mL of Et_2O (0.028 M) under argon atmosphere and subsequently cooled to 0 ºC. Then $LiAlH_4$ was slowly added (7.5 mg, 0.463 mmol, 2 equiv.) to the reaction mixture and the reaction was stirred at 0 ºC for 1 h until all starting materials were consumed which was monitored by TLC 100 % EtOAc) and allowed to continue for 15 more minutes at 0 ºC. (total reaction time typically about 1 h). The reaction was quenched by slow, dropwise addition of 8 mg of H_2O, followed by slow, dropwise addition of 8 mg of 15 % NaOH (aq), and finishing with an addition of 24 mg of H_2O. At this point, the mixture is allowed to reach room temperature until all salts appear to become a white color. SiO_2 was then added and the solvent removed, and was placed on a short silica gel plug and eluted with a 100 % EtOAc: acetone mixture, producing 20.2 mg (77% yield) of triol **2.158**.

(1*S*,6*R*,8*R*)-8-((*R*)-2-((triethylsilyl)oxy)but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.153)



To the solution of phosphate **2.141** (100 mg, 0.406 mmol) in 4 mL of CH_2Cl_2 (0.1M) was added 2,6-lutidine (95 µL, 0.923 mmol, 2.0 equiv.). The solution was then cooled to 0 ºC and TESOTf (140 µL, 0.609 mmol, 1.5 equiv.) was added dropwise to the solution. The solution was stirred at 0 ºC until completion (about 1 hour). The reaction was quenched with 3 mL of saturated aqueous NH_4Cl, layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were then washed with brine, dried with $MgSO_4$. Purification by flash chromatography (1:2 hexane/ethyl acetate) provided 101 mg (90 % yield) of the silyl protected phosphate **2.153** as a white crystalline solid.

R_f = 0.25 (1:2 hexane/ethyl acetate);

M.P: 112–116 ºC;

FTIR (thin film): 2955, 2914, 2876, 1630, 1294, 1263, 1236, 1220, 1134, 1074, 1061, 978 cm-1;

Optical Rotation: $[\alpha]_D$ = -36.4 (*c* = 1.05, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.00 (dddd, *J* = 11.9, 6.7, 3.6, 2.4 Hz, 1H), 5.80 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.56 (ddd, 11.9, 3.9, 2.6 Hz, 1H), 5.30 (dd, *J* = 17.3, 1.1 Hz,

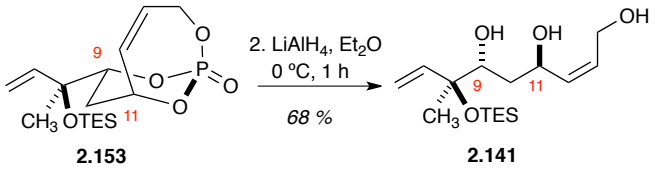
1H), 5.21 (dddd, J = 25.0, 2.5, 1.9, 1.7 Hz, 1H), 5.17 (dd, J = 10.7, 1.1 Hz, 1H), 4.99 (dddd, J = 14.7, 5.6, 5.5, 2.7 Hz, 1H), 4.34 (ddd, J = 27.7, 14.2, 6.8 Hz, 1H), 4.24 (ddd, J = 11.9, 1.8, 1.7 Hz, 1H), 2.31 (ddd, J = 14.7, 11.9, 6.4 Hz, 1H), 1.79 (ddd, J = 13.1, 2.4, 1.8 Hz, 1H), 1.40 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.61 (qd, J =7.2, 1.6 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.0, 130.3, 128.0, 115.7, 81.5 (d, J_{CP} = 7.6 Hz), 77.4 (d, J_{CP} = 6.6 Hz), 76.4 (d, J_{CP} = 10.0 Hz), 63.2 (d, J_{CP} = 6.4 Hz), 29.0 (d, J_{CP} = 5.4 Hz), 22.7, 7.3 (3C), 6.9 (3C);

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.89 (t, J_{PH} = 27.0 Hz);

HRMS cald for $C_{16}H_{29}NaO_5PSi$ $(M+Na)^+$ 383.1420; found 383.1423 (TOF MS ES+).

(4*R*,6*R*,7*R*,*Z*)-7-methyl-7-((triethylsilyl)oxy)nona-2,8-diene-1,4,6-triol (2.141).



To the phosphate **2.153** (40.0 mg, 0.111 mmol) was added 3.9 mL of THF (0.028 M) under argon atmosphere and subsequently cooled to 0 ºC. To this solution $LiAlH_4$ (12 mg, 0.333 mmol, 3 equiv.) was slowly added and allowed to continue stirring at 0 ºC until all the starting material consumed (monitored by TLC 1:2 Hexane/EtOAc). The reaction was quenched by slow, dropwise addition of 13 μL of H_2O, followed by slow, dropwise addition of 13 μL of 15 % NaOH (aq), and finishing with an addition of 39 μL of H2O. At this point, the mixture is allowed to reach room temperature until all salts appear to have become a white color. SiO_2 was then added and the solvent removed, and was placed on a short silica gel plug and eluted with a 1:4 Hexane/EtOAc mixture, producing 150 mg (68% yield) of mono-protected tetraol **2.141**.

R_f = 0.2 (1:3 hexane/ethyl acetate);

FTIR (thin film): 3342, 2955, 2912, 2877, 1630, 1458, 1413, 1049, 1010, 977 cm-1;

Optical Rotation: $[\alpha]_D$ = +17.4 (*c* = 2.20, CH_2Cl_2);

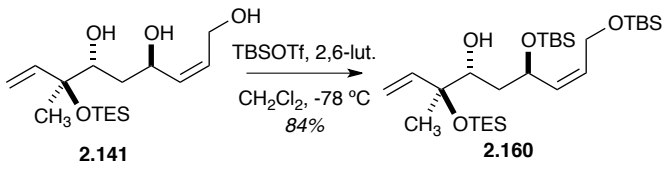
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.93 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.69 (dddd, *J* = 6.3, 5.0, 1.2, 1.1 Hz, 1H), 5.57 (ddt, *J* = 11.2, 7.8, 1.3 Hz, 1H), 5.31 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.13 (dd, *J* = 10.9, 1.4 Hz, 1H), 4.67 (dd, *J* = 8.4, 8.3 Hz, 1H), 4.28 (ddd, *J* = 7.0, 6.7, 6.1 Hz, 1H), 4.18 (ddd, *J* = 8.6, 7.1, 5.9 Hz, 1H), 3.82 (dd, *J* = 7.1, 3.9 Hz, 1H), 3.77

(br s, 1H), 3.63 (m, 1H), 1.80 (ddd, J = 14.8, 6.7, 3.8 Hz, 1H), 1.58 (br s, 1H), 1.54 (ddd, J = 14.8, 7.0, 2.7 Hz, 1H), 1.27 (s, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.69 (q, J = 8.0 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.0, 135.7, 130.0, 113.5, 76.2, 75.7, 65.3, 59.0, 40.6, 25.0, 7.2 (3C), 5.4 (3C);

HRMS cald for $C_{16}H_{32}NaO_4Si$ (M+Na)+ 339.1968; found 339.1970 (TOF MS ES+).

(5*S*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol (2.160)



To the solution of triol **2.160** (15 mg, 0.05 mmol) in 0.5 mL of CH_2Cl_2 (0.1M) was added 2,6-lutidine (25 µL, 0.21 mmol, 4.5 equiv.). The solution was then cooled to -78 ºC and TBSOTf (24 µL, 0.10 mmol, 2.2 equiv.) was added dropwise to the solution with stirring. The solution was stirred at -78 ºC for 2h, until all the starting materials were consumed, monitored by TLC (4:1 Hexane/EtOAc). The reaction was diluted with 1 mL of CH_2Cl_2 and quenched with 0.5 mL of saturated aqueous NH_4Cl, and layers were separated, and the aqueous layer was extracted 3 more times with CH_2Cl_2. The combined organic layers were then washed with brine, dried with $MgSO_4$. Purification by flash chromatography (hexane: ethyl acetate) provided bis-TBS protected monoalcohol **2.160** (25 mg, 84% yield) as a yellow oil.

R_f = 0.3 (4:1 hexane/ethyl acetate);

FTIR (thin film): 3464, 3016, 2954, 2929, 2879, 2858, 1620, 1471, 1362, 1254, 1080 cm-1;

Optical Rotation: $[\alpha]_D$ = +4.4 (*c* = 3.34, CH_2Cl_2);

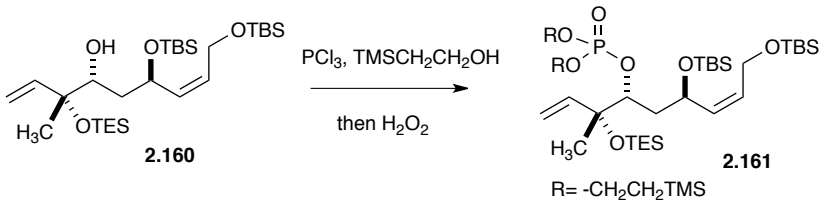
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.93 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.48 (ddd, *J* = 10.8, 5.1, 5.0 Hz, 1H), 5.37 (ddd, *J* = 11.2, 6.2, 1.6 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.6 Hz, 1H), 5.10 (dd, *J* = 10.8, 1.6 Hz, 1H), 4.48 (ddd, *J* = 9.4, 3.8, 3.6 Hz, 1H), 4.29 (ddd, *J* =

13.1, 7.0, 1.6 Hz, 1H), 4.13 (ddd, *J* = 13.1, 5.3, 1.7 Hz, 1H), 3.68 (dd, *J* = 5.8, 3.8 Hz, 1H), 2.59 (s, 1H), 1.90 (ddd, *J* = 14.5, 9.7, 3.8 Hz, 1H), 1.31 (dddd, *J* = 9.8, 5.8, 4.9, 3.9 Hz, 1H), 1.21 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.66 (qd, *J* = 8.0,1.9 Hz, 6H), 0.07 (s, 9H), 0.05 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.3, 134.0, 129.7, 113.3, 75.9, 75.5, 66.8, 59.6, 43.0, 25.8(7C), 23.8, 18.5, 18.3, 7.0(3), 5.7(3), -3.4, -4.5, 5.2;

HRMS cald for $C_{28}H_{60}NaO_4Si_3$ $(M+Na)^+$ 567.3697; found 567.3688 (TOF MS ES+).

(5*R*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-yl-bis(2-(trimethylsilyl)ethyl) phosphate (2.161)



A solution of the alcohol **2.160** (5.9 mg, 0.018 mmol) in pyridine (0.6 mL) was cooled to 0 ºC, and a freshly prepared solution of PCl_3 (2 M in CH_2Cl_2, 2 μL, 0.02 mmol) was added to the stirred solution in one portion via syringe. After 10 min at 0 ºC, freshly distilled 2-trimethylsilylethanol (15.5 μL) and a catalytic amount of DMAP (~0.1 mg) were added and mixture was warmed to RT over 1 h. Reaction was diluted with CH_2Cl_2 (0.6 mL) and 30% aqueous hydrogen peroxide (43 μL) were added, and stirring was continued for 2 h at 23 ºC. The mixture was poured into 0.5N HCl (0.5 mL) and extracted with CH_2Cl_2 (3 x 2 mL) Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography afforded **2.161** (6.6 mg, 74 % yield) as yellow oil.

R_f = 0.2 (10:1 Hexane/EtOAc);

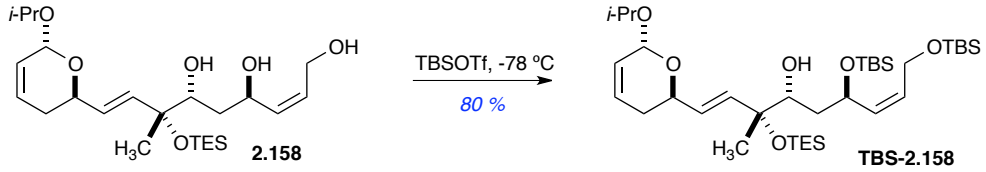
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.04 (dd, *J* = 10.9, 17.6 Hz 1H), 5.47–5.43 (m, 1H), 5.37 (d, *J* = 9.4 Hz, 1H), 5.31 (dd, *J* = 11.8, 1.8 Hz, 1H), 5.28 (d, *J* = 5.9 Hz, 1H), 4.47 (t, *J* = 8.8 Hz, 1H), 4.32 (dd, *J* = 13.2, 6.8 Hz, 2H), 4.08 (m, 4H), 3.87 (d, *J* = 7.7 Hz,

1H), 1.78–1.68 (m, 1H), 1.58 (s, 3H), 1.26 (s, 4H), 1.23 (m, 1H) 1.09 (m, 18H), 0.98 (m, 12H), 0.90 (m, 18H), 0.72 – 0.63 (m, 6H), 0.05 (t, J = 4.0 Hz, 9H);

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -0.55 and -4.29;

HRMS cald for $C_{38}H_{86}O_7PSi_5$ $(M+H)^+$ 825.4958; found 825.4905 (TOF MS ES+)

(5*R*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5-((*E*)-2-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)vinyl)-5,13,13,14,14-pentamethyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol (TBS-2.158)



To the solution of triol **2.158** (32 mg, mmol) in 1.0 mL of CH_2Cl_2 (0.1M) was added 2,6-lutidine (52 µL, 4.4 mmol, 4.5 equiv.). The solution was then cooled to -78 ºC and TBSOTf (50 µL, 0.22 mmol, 2.2 equiv.) was added dropwise to the solution with stirring. The solution was stirred at -78 ºC for 2 h, until all the starting materials were consumed, monitored by TLC (8:1 Hexane/EtOAc). The reaction was diluted with 2 mL of CH_2Cl_2 and quenched with 1 mL of saturated aqueous NH_4Cl, and warmed to rt. The layers were separated, and aqueous layer was extracted 3 more times with CH_2Cl_2. The combined organic layers were then washed with brine, dried with $MgSO_4$. Purification by flash chromatography (8:1 Hexane:EtOAc) provided 53 mg of the bis TBS protected product **TBS-2.158** as a yellow oil in 80 % yield.

R_f = 0.5 (8:1 Hexane/EtOAc);

FTIR (thin film): 3340, 3417, 2955, 2858, 2707, 1650, 1080, 837 cm-1;

Optical Rotation: $[\alpha]_D$ = +29 (*c* = 0.2, $CHCl_3$);

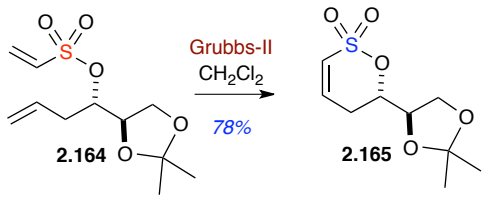
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.01 (dd, *J* = 9.9, 5.2 Hz, 1H), 5.87–5.77 (m, 2H), 5.73 (dtd, *J* = 10.0, 2.8, 1.3 Hz, 1H), 5.48 (ddd, *J* = 11.5, 6.3, 5.4 Hz, 1H), 5.36 (ddd, *J* =

10.8, 3.1, 1.5 Hz, 1H), 5.11 (s, 1H), 4.51 (dd, *J* = 9.5, 3.1 Hz, 1H), 4.48–4.42 (m, 1H), 4.31 (ddd, *J* = 13.2, 7.1, 1.5 Hz, 1H), 4.15 (ddd, *J* = 13.2, 5.2, 1.7 Hz, 1H), 4.00 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.73 (dd, *J* = 6.1, 3.4 Hz, 1H), 2.64 (s, 1H), 2.14–1.97 (m, 2H), 1.89 (ddd, *J* = 14.5, 10.1, 3.4 Hz, 1H), 1.56 (s, 1H), 1.30 (ddd, *J* = 14.6, 6.1, 3.4 Hz, 2H), 1.24–1.22 (m, 6H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.93–0.87 (m, 20H), 0.67 (ddd, *J* = 11.0, 7.9, 2.6 Hz, 6H), 0.08 (s, 8H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 135.0, 133.7, 129.5, 128.7, 128.6, 126.1, 93.2, 75.8, 74.7, 69.5, 66.6, 66.2, 59.3, 42.7, 30.6, 25.9 (6C), 23.9 (2C), 22.1, 18.3, 18.1, 7.0 (3C), 5.5 (3C), -3.3, -4.5, -5.2 (2C);

HRMS cald for $C_{36}H_{72}O_6PSi_3Na$ $(M+Na)^+$ 707.4534; found 707.4530 (TOF MS ES+).

(*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-1,2-oxathiine 2,2-dioxide (2.165).



To a stirring solution of diene **2.164** (2.01 g, 7.703 mmol) in freshly distilled, CH_2Cl_2 (700 mL, 0.011 M) was added Grubbs–II catalyst (196 mg, 0.231 mmol) and the reaction was refluxed for 1 h until all the starting materials were consumed (monitored by TLC 2:1 Hexane/EtOAc). Reaction was cooled to RT and concentrated under reduced pressure. Purification by flash chromatography afforded the RCM product **2.165** (1.5 g, 78% yield) as a white crystalline solid.

R_f = 0.2 (2:1 Hexane/EtOAc);

M.P: 1105–107 ºC;

FTIR (thin film): 3066, 2987, 2937, 2894, 1625, 1419, 1352, 1182, 1066, 894, cm-1;

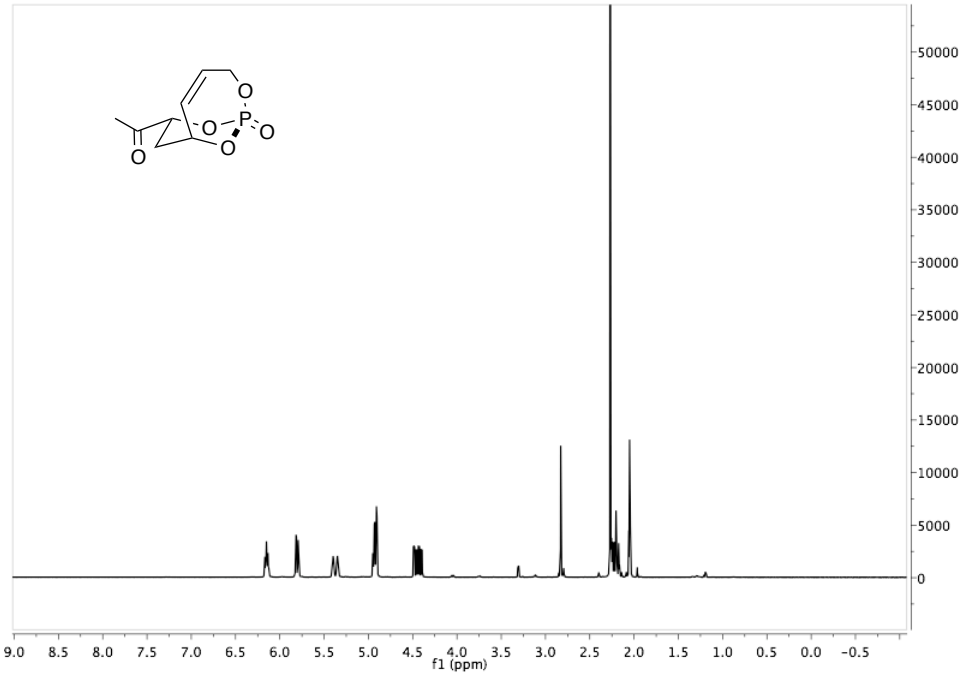
Optical Rotation: $[\alpha]_D$ = –0.9 (*c* = 2.27, $CHCl_3$);

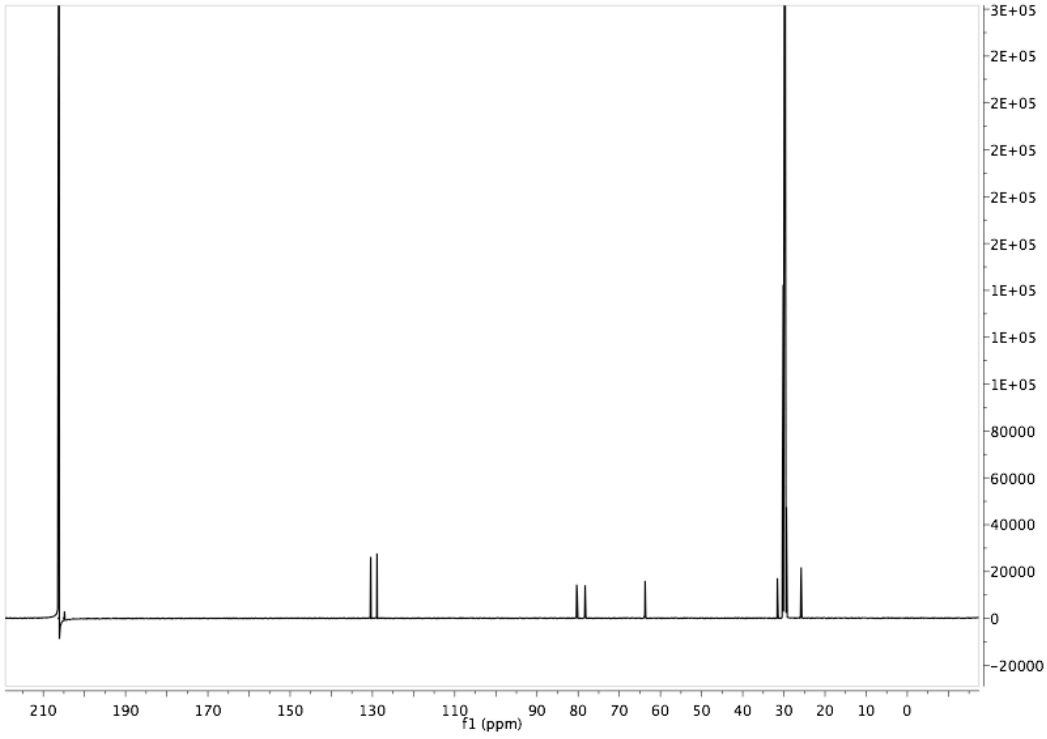
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm); 6.57 (s, 2H), 4.80 (ddd, *J* = 9.7, 7.6, 4.9 Hz, 1H), 4.24–4.19 (m, 2H), 4.04 (dd, J = 8.9, 4.0 Hz, 1H), 2.57 (ddd, *J* = 8.0, 4.2, 2.5 Hz, 2H), 1.44 (s, 3H), 1.37 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 136.7, 126.2, 110.6, 81.1, 75.9, 66.5, 27.2, 26.7, 24.9;

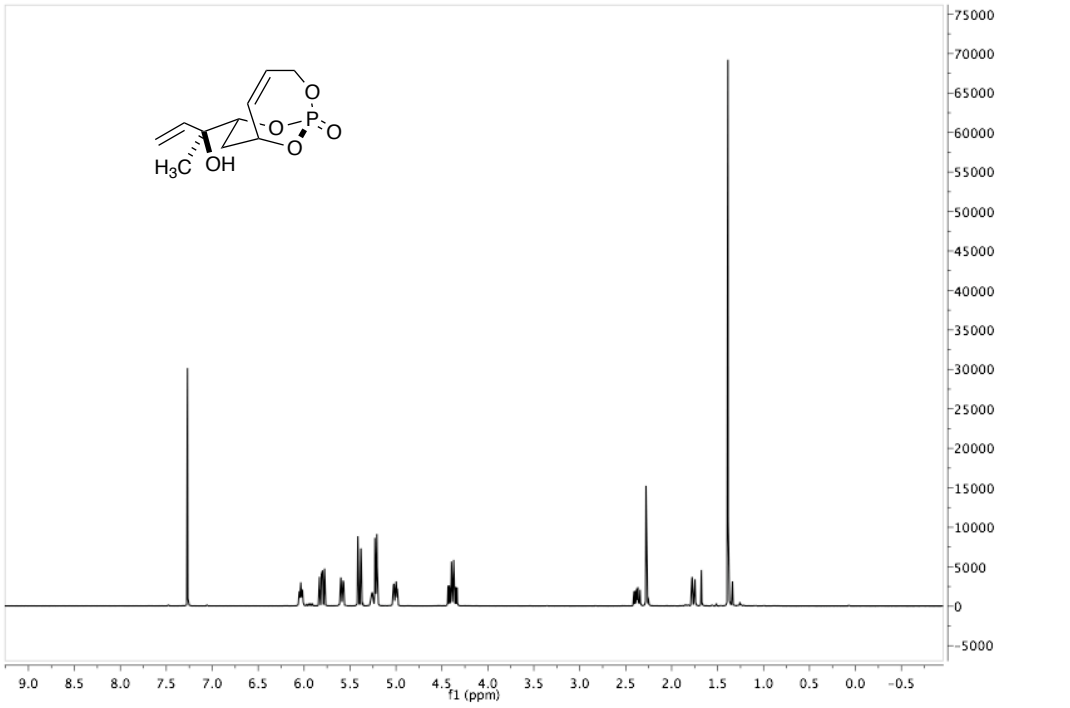
HRMS cald for $C_9H_{14}O_5PSNa$ (M+Na)+ 257.0460; found 257.0420 (TOF MS ES+).

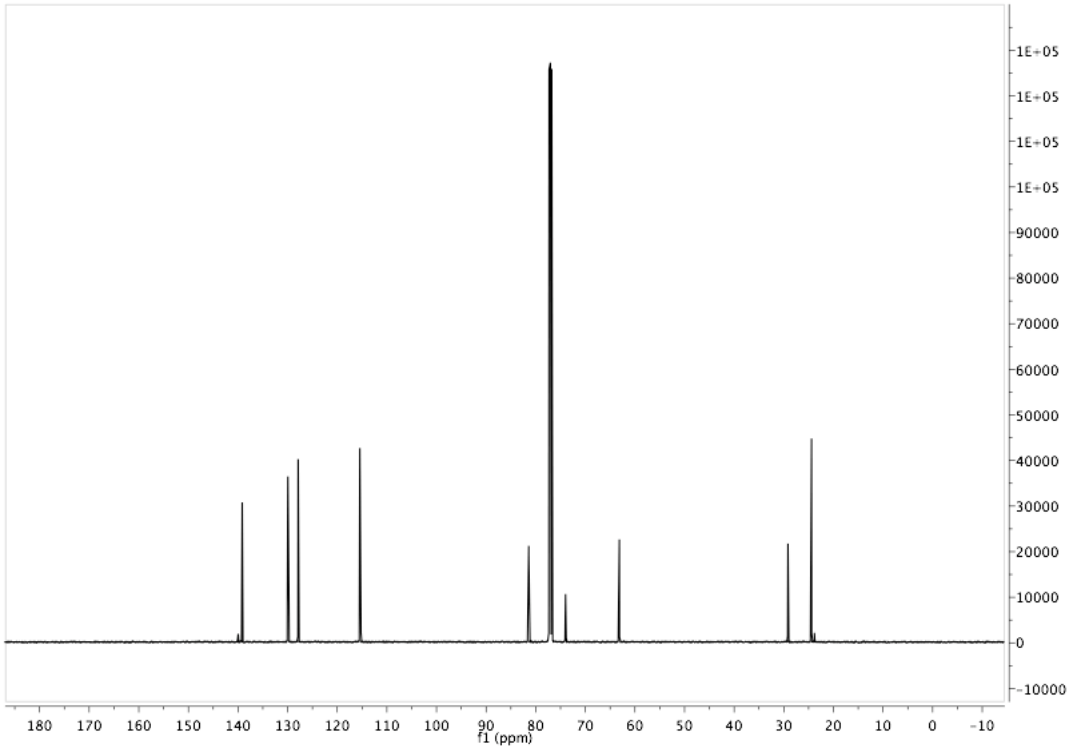
1-((1*S*, 6*R*, 8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)ethanone(2.103)

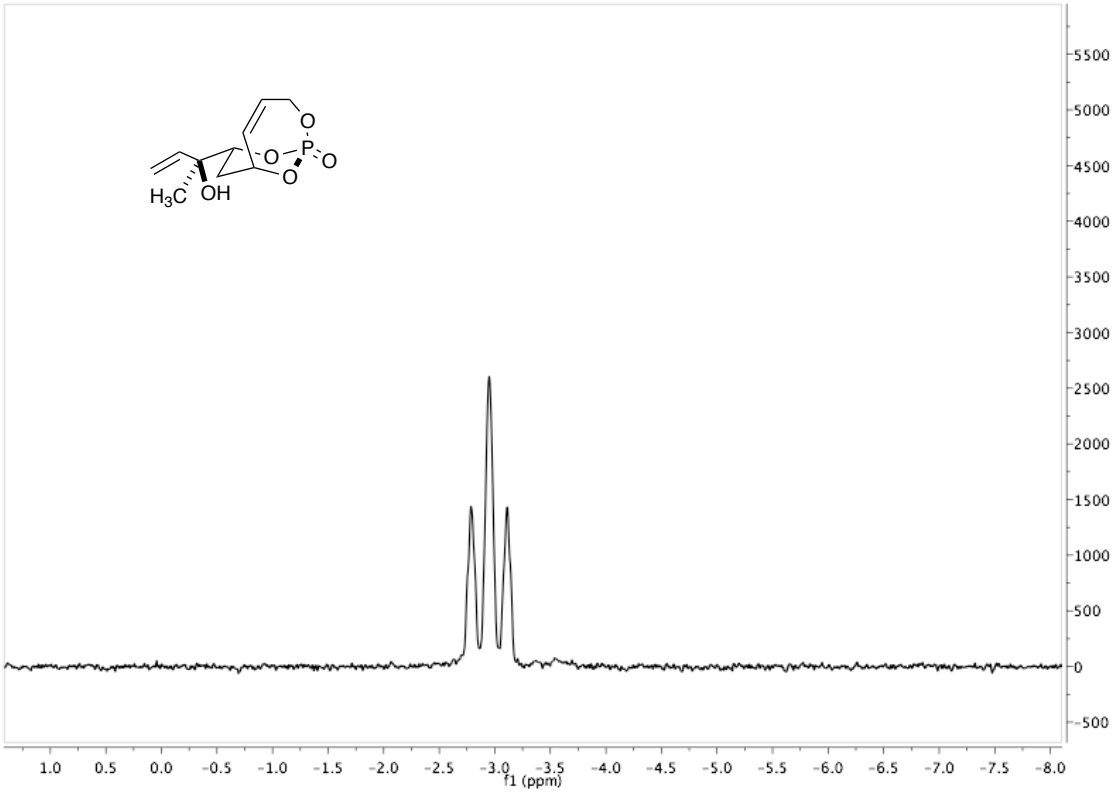




(*R*)-2-((1*S*,6*R*,8*R*)-1-oxo-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-ol(2.104)



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0.0
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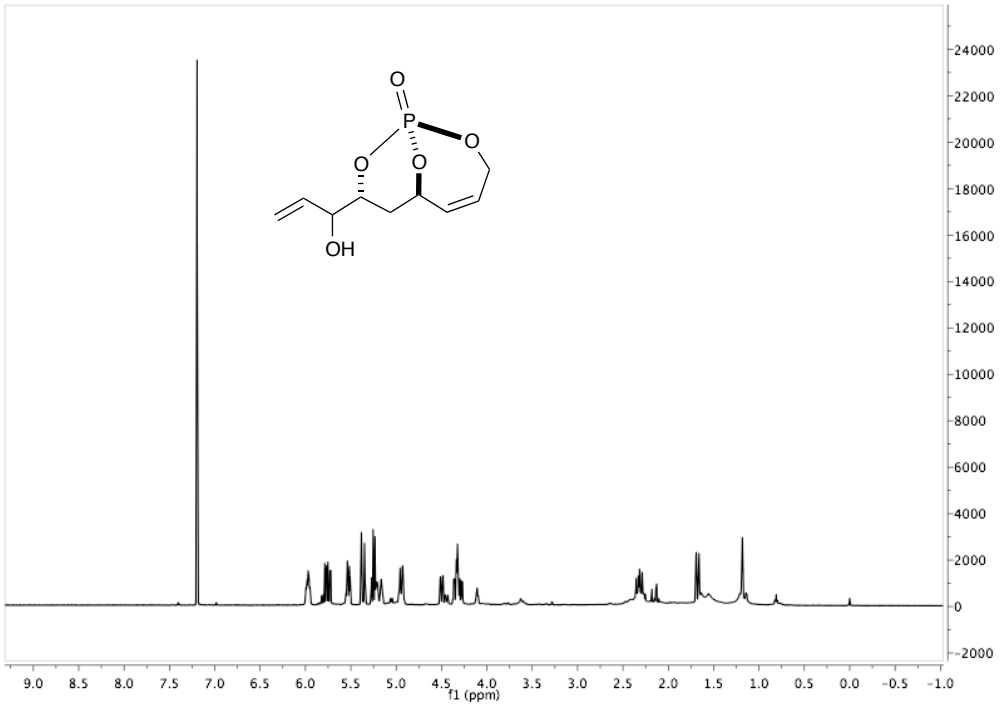
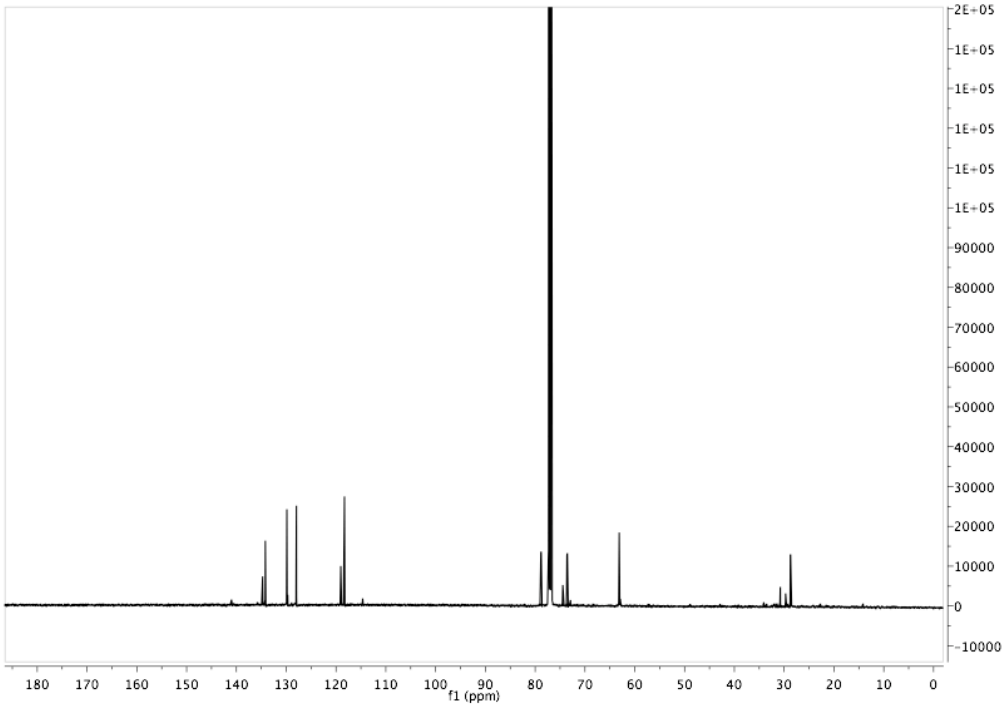
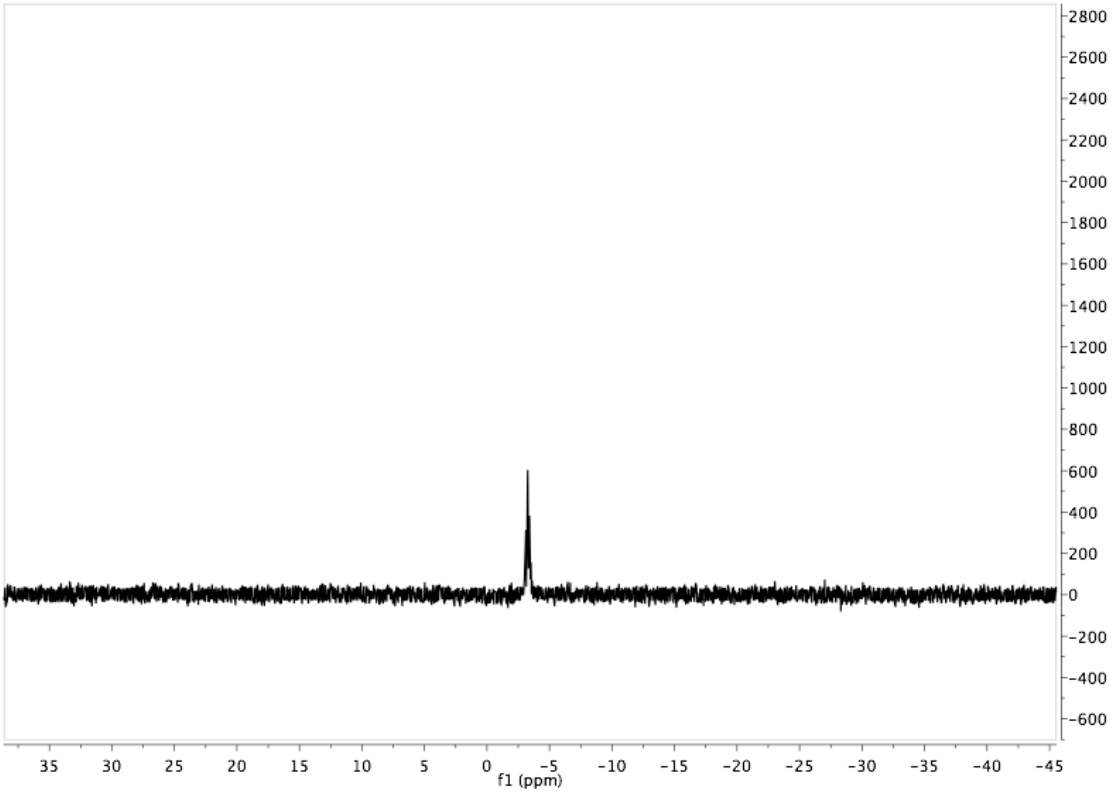
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
-8.0
f1 (ppm)

(1*S*,6*R*,8*R*)-8-(1-hydroxyallyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.114)



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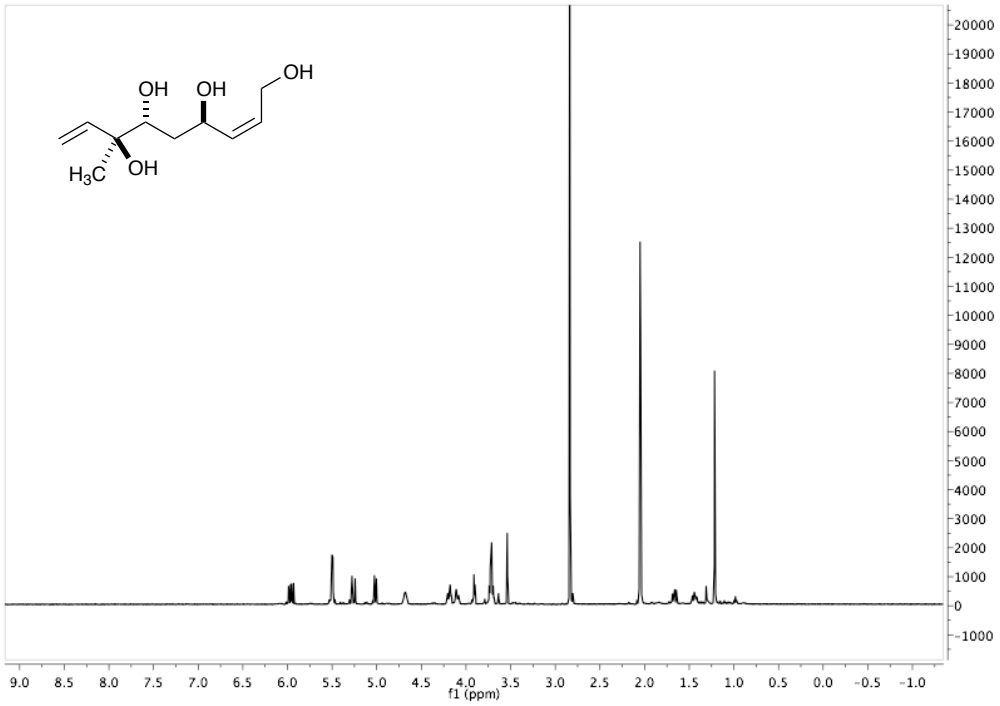
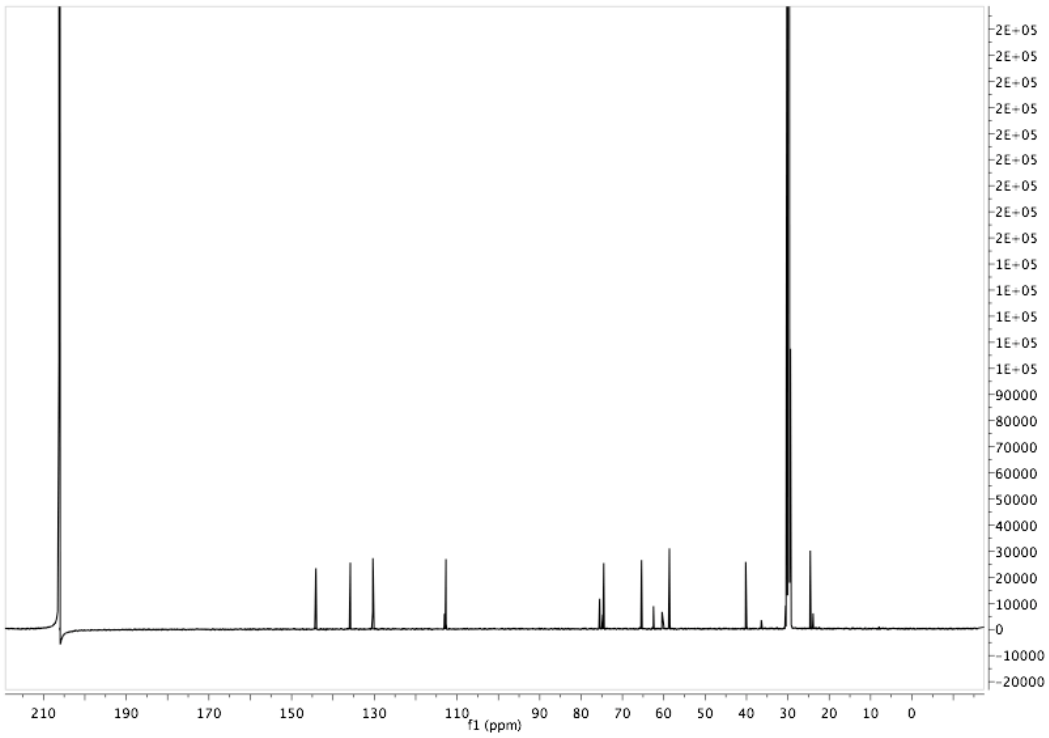
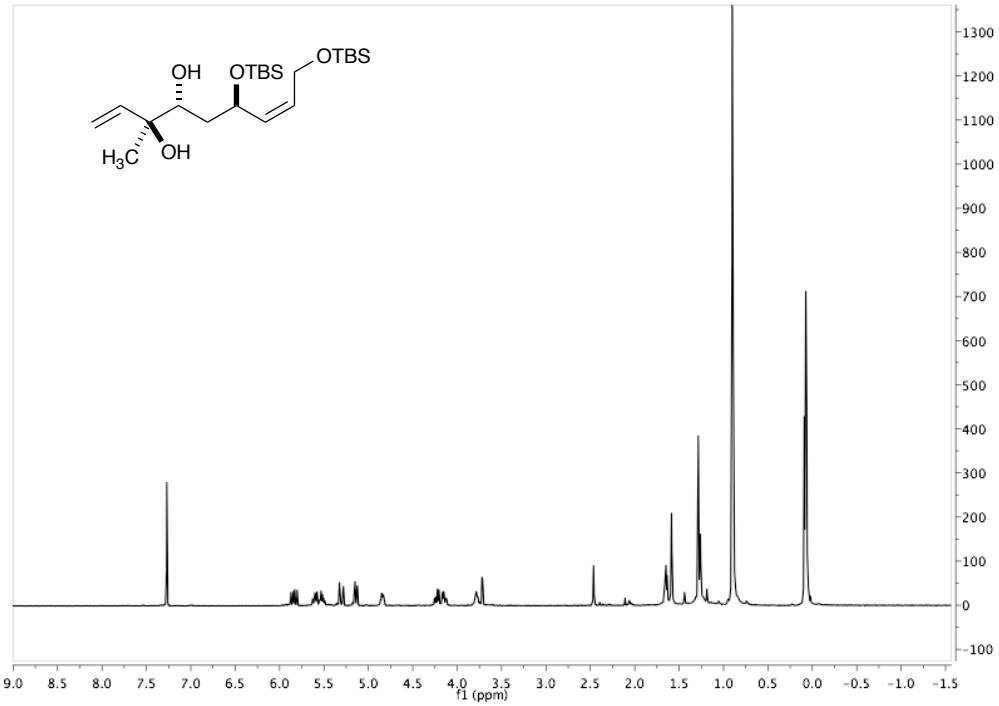
30
25
20
15
10
5
0
−5
−10
−15
−20
−25
−30
−35
−40
−45
f1 (ppm)

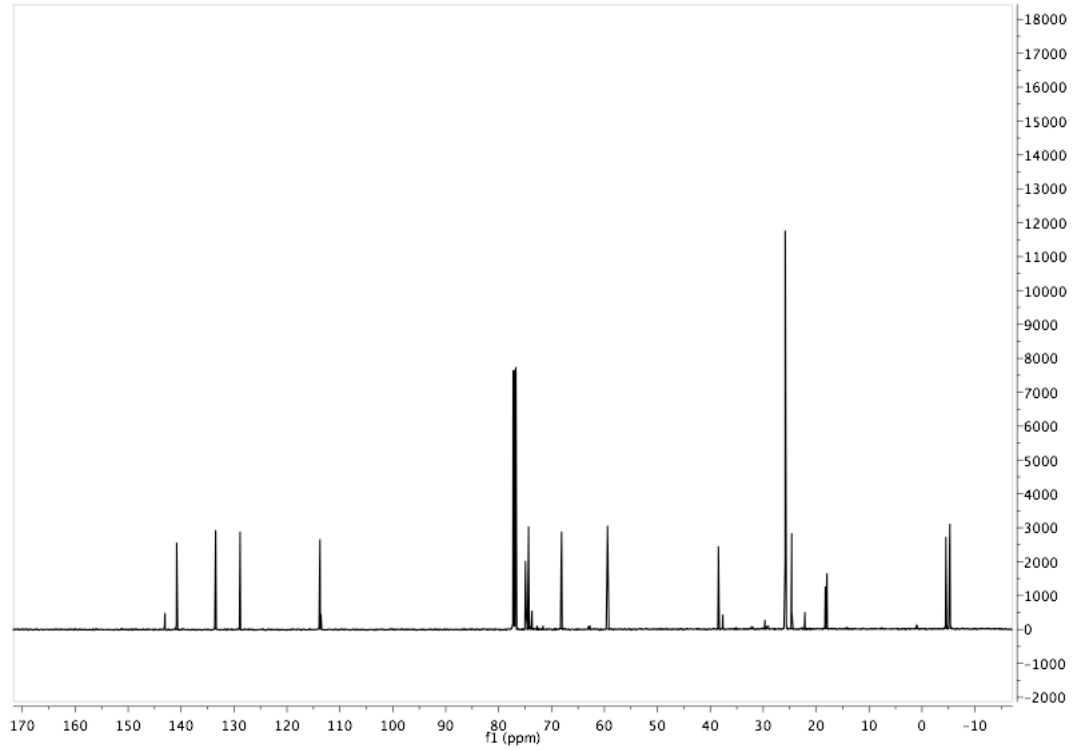
(4*R*,6*R*,7*R*,*Z*)-7-methylnona-2,8-diene-1,4,6,7-tetraol (2.142)



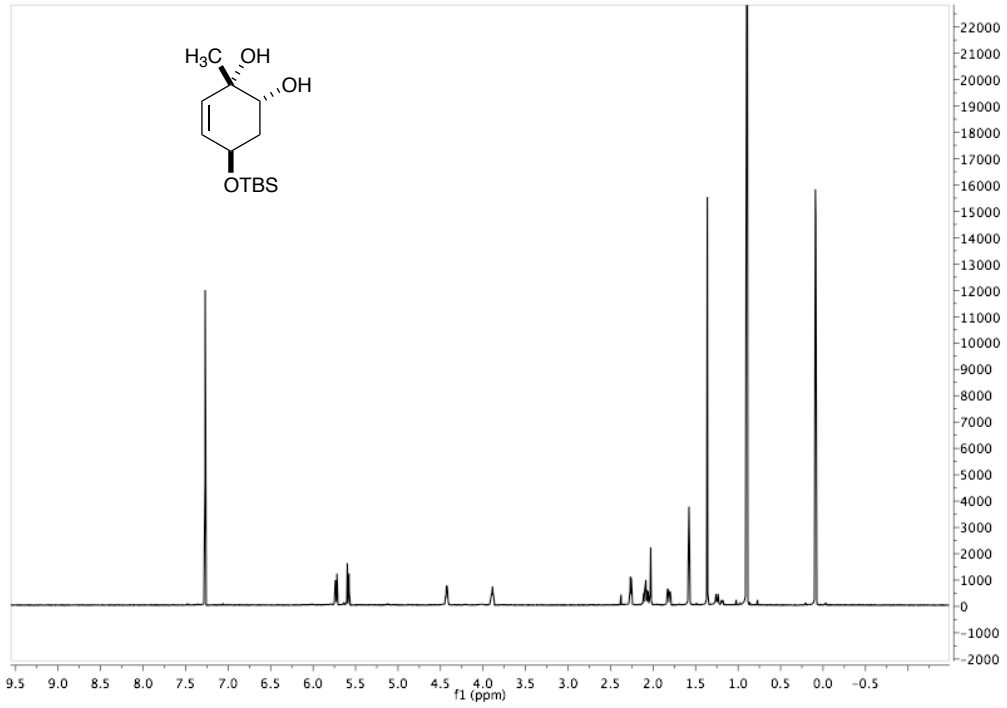


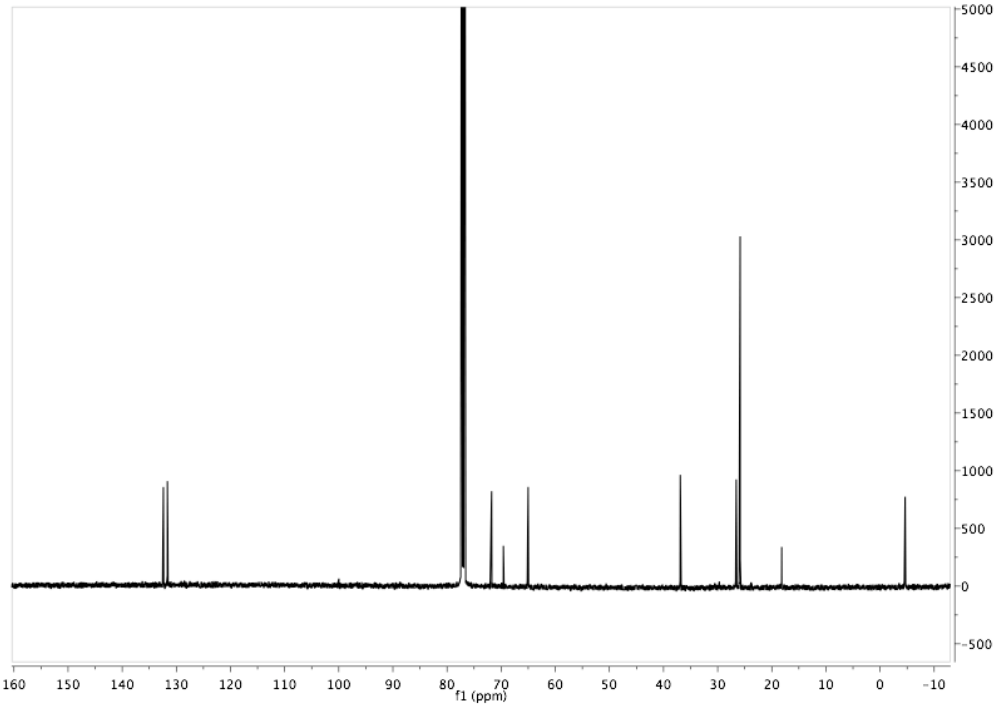
(3*S*,4*R*,6*R*,*Z*)-6,9-bis((*tert*-butyldimethylsilyl)oxy)-3-methylnona-1,7-diene-3,4-diol (2.143)



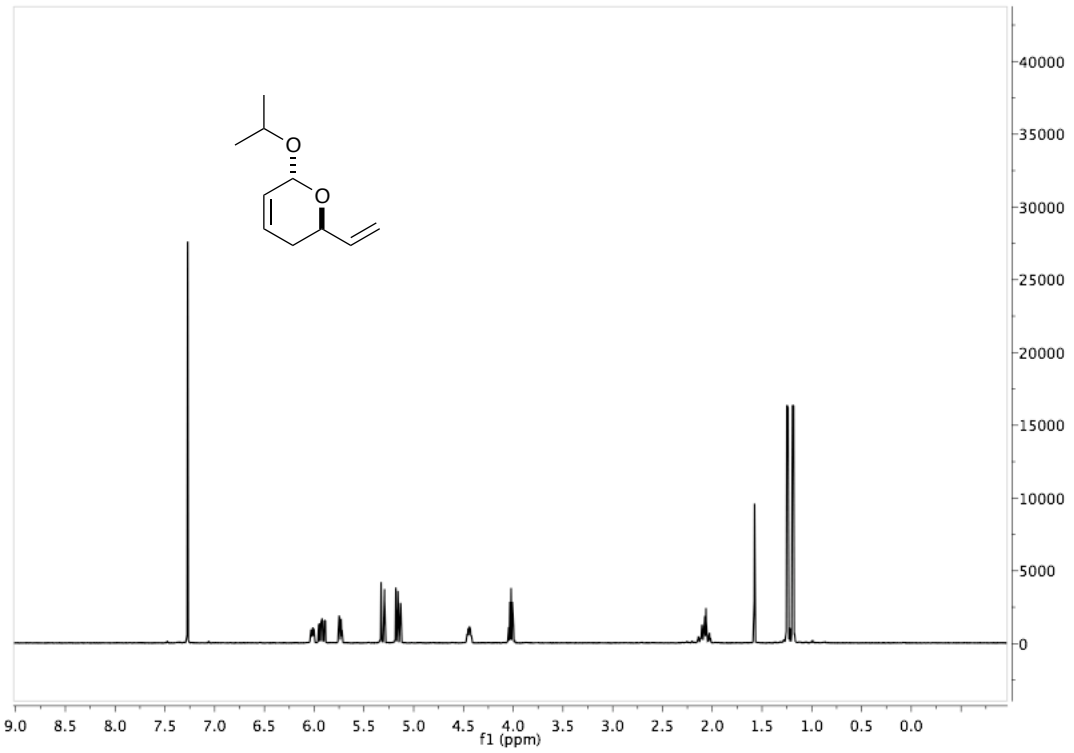


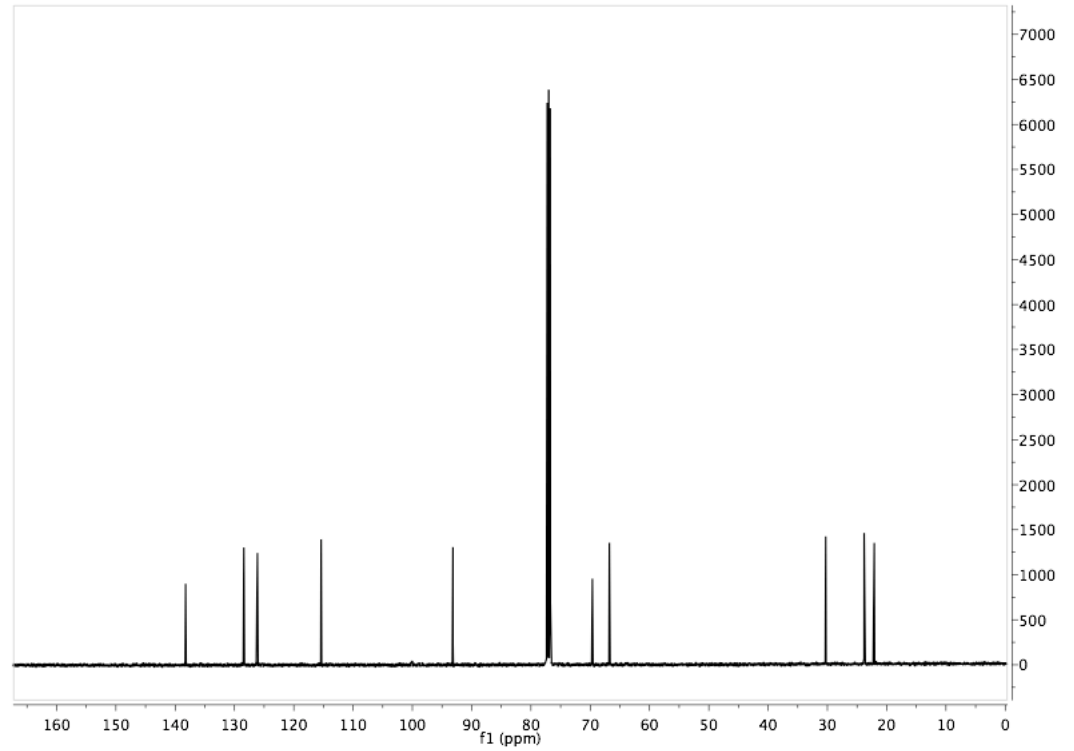
(1*R*,2*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylcyclohex-3-ene-1,2-diol (2.146)



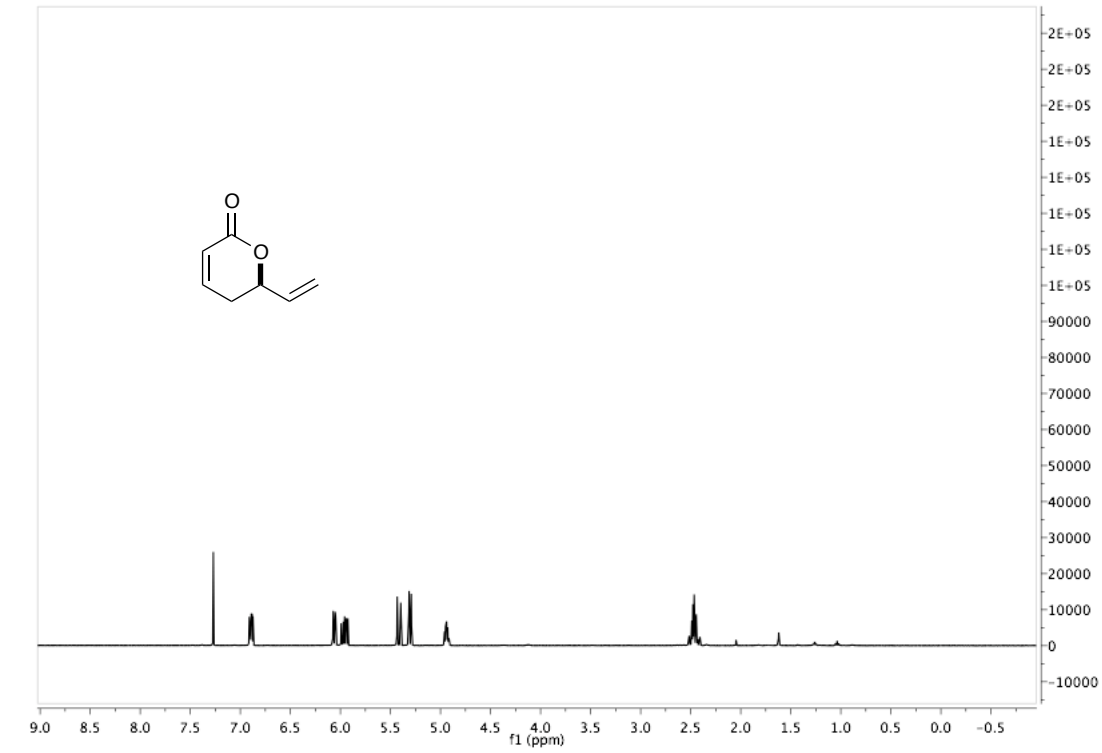


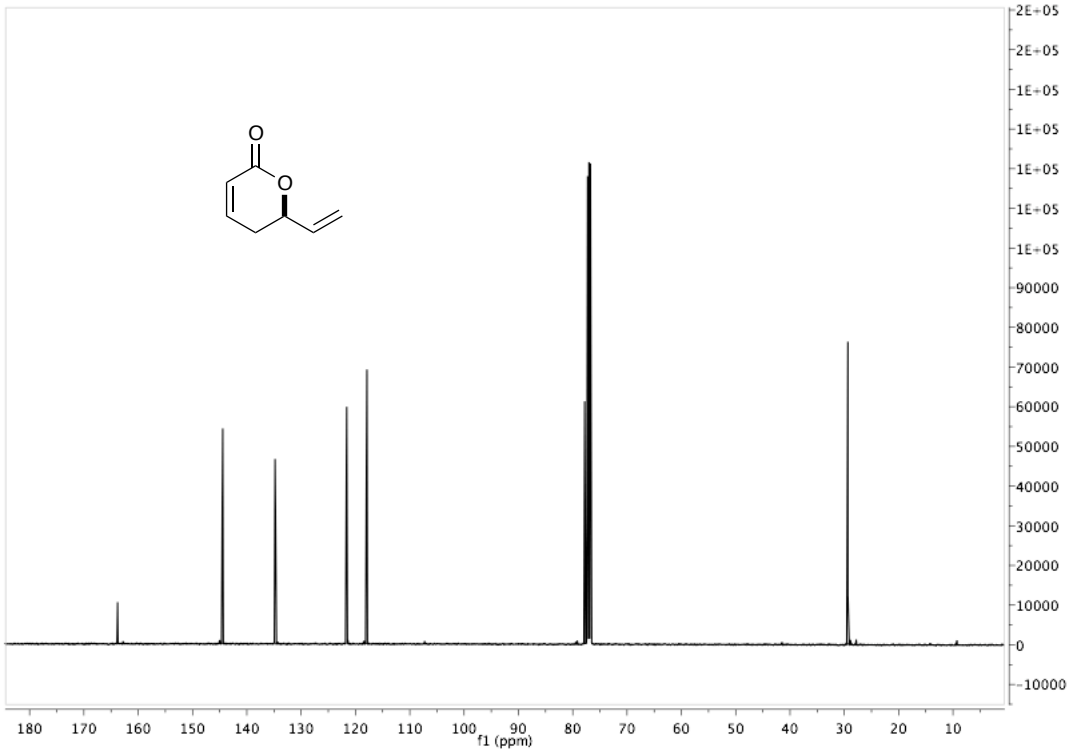
(2*R*,6*R*)-6-isopropoxy-2-vinyl-3,6-dihydro-2*H*-pyran (2.97)



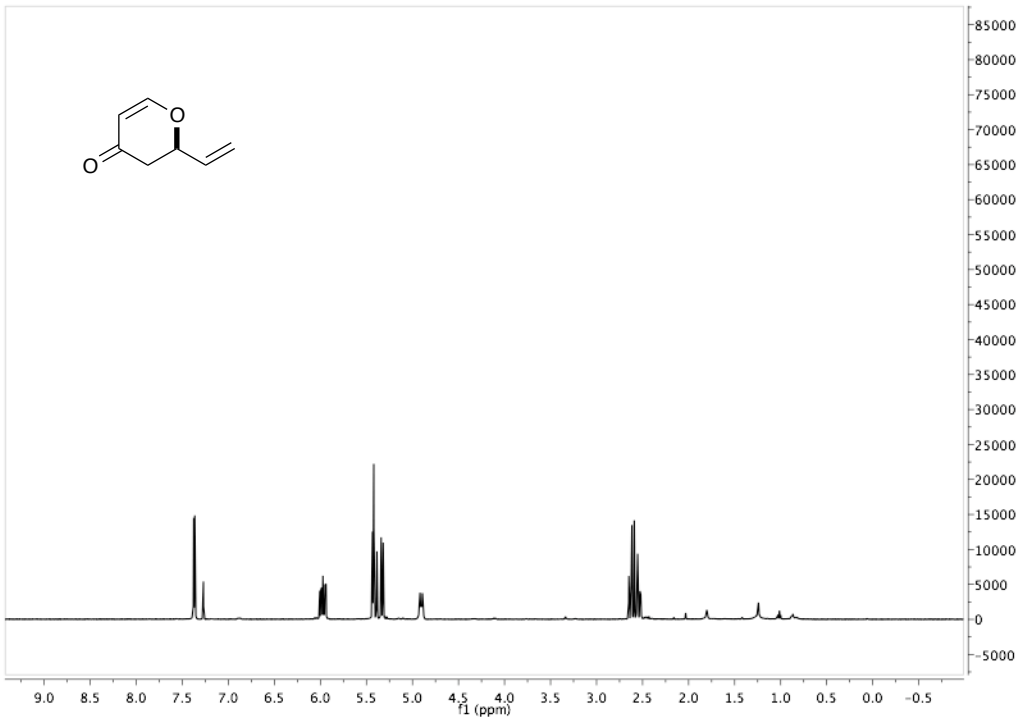


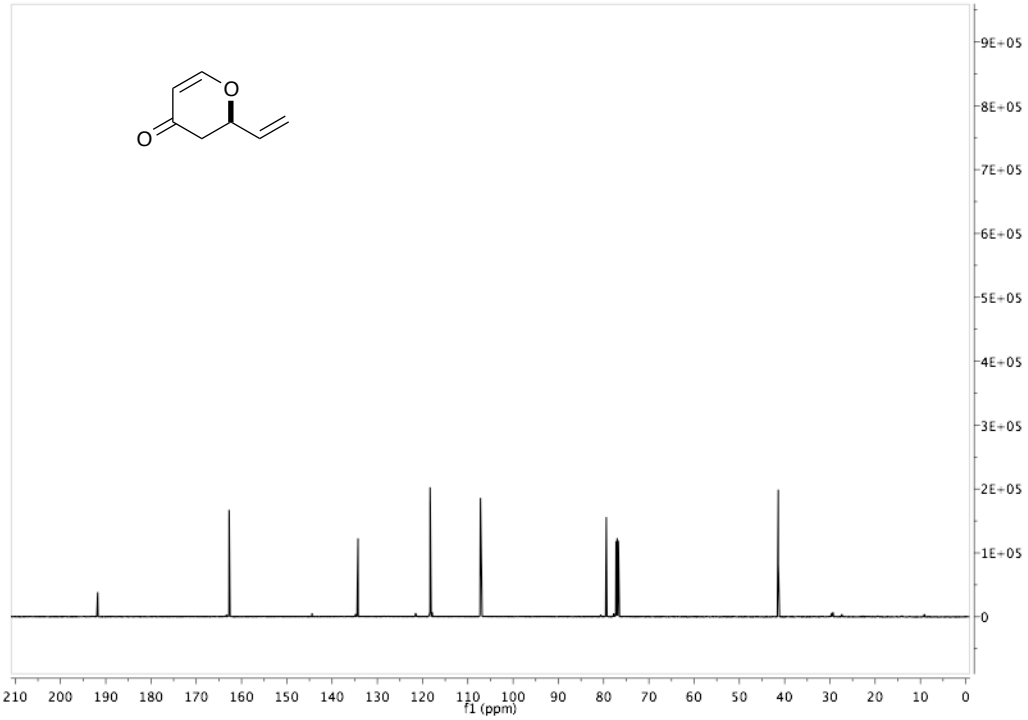
(*R*)-6-vinyl-5, 6-dihydro-2*H*-pyran-2-one (2.98)



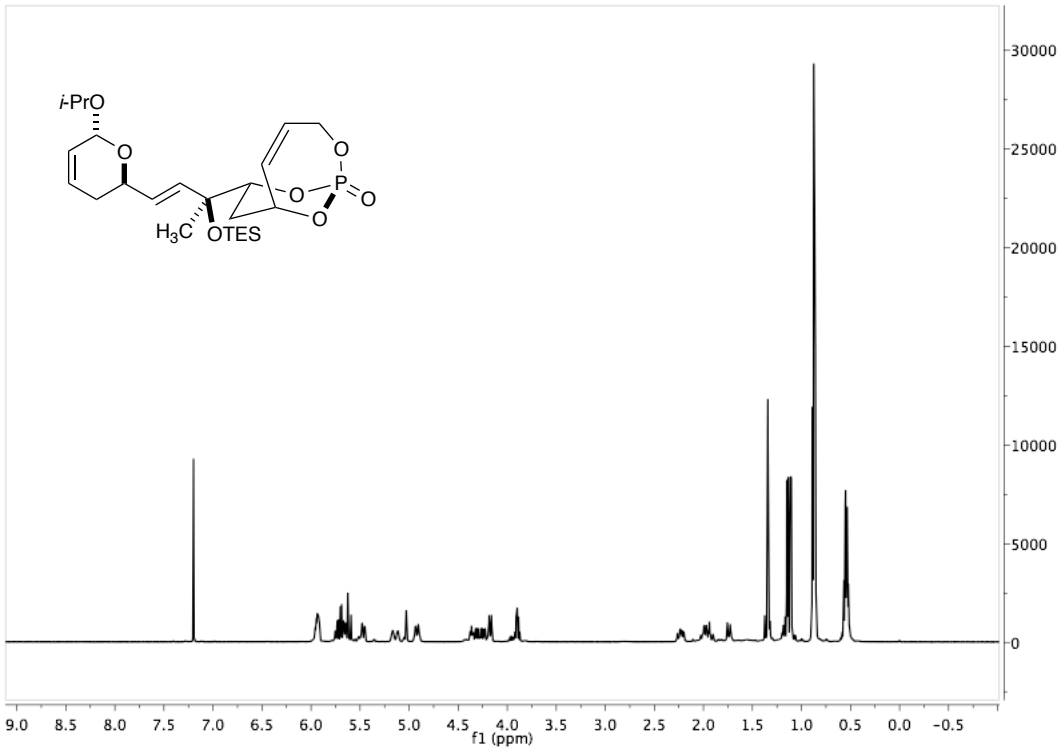


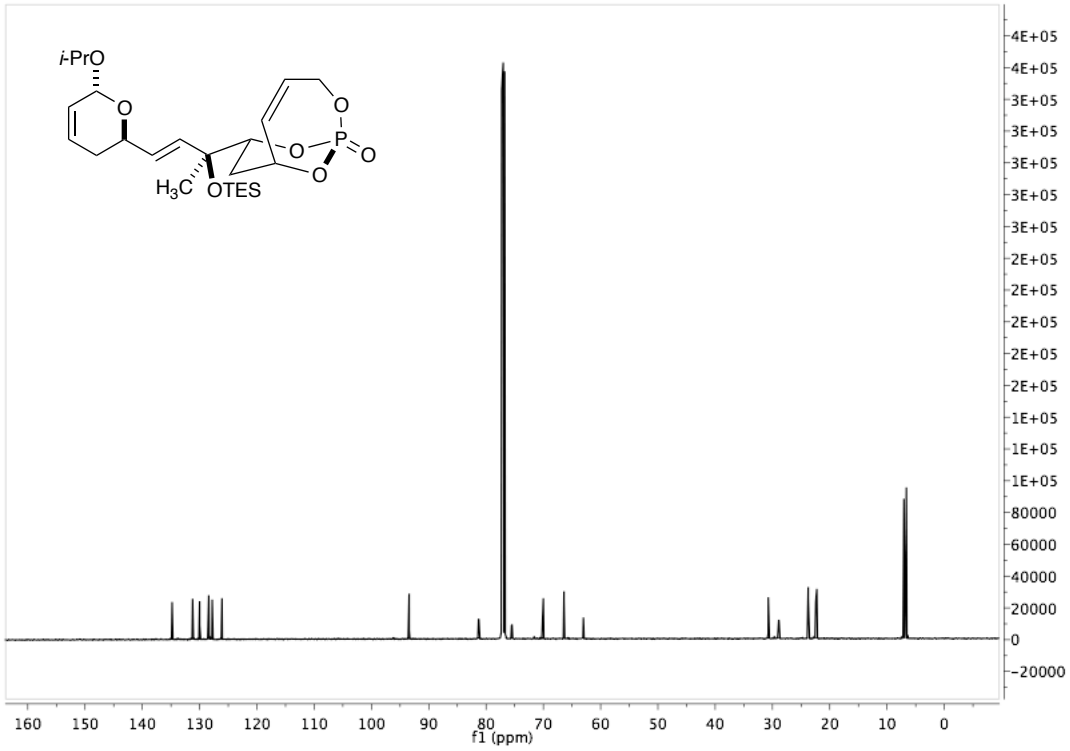
(*R*)-2-vinyl-2*H*-pyran-4(3*H*)-one (2.129).





(1*S*,6*R*,8*R*)-8-((*S*,*E*)-4-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-2-((triethylsilyl)oxy)but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (2.154)

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P
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H3C
OTES
4E+05
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2E+05
2E+05
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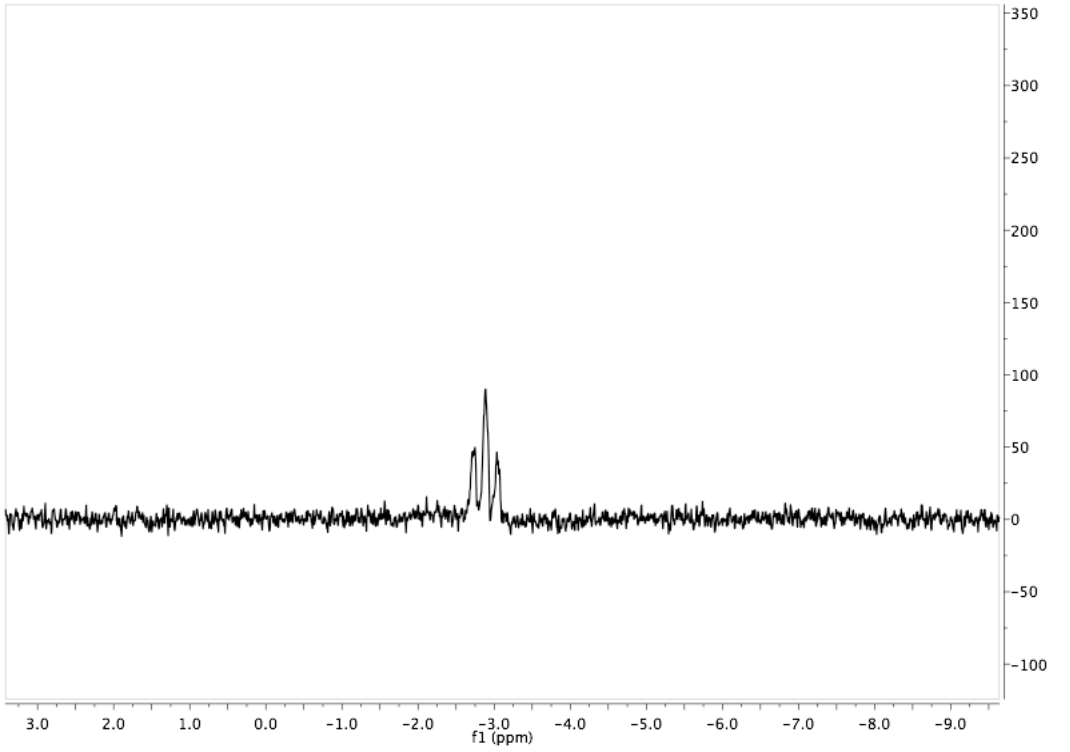
f1 (ppm)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-100
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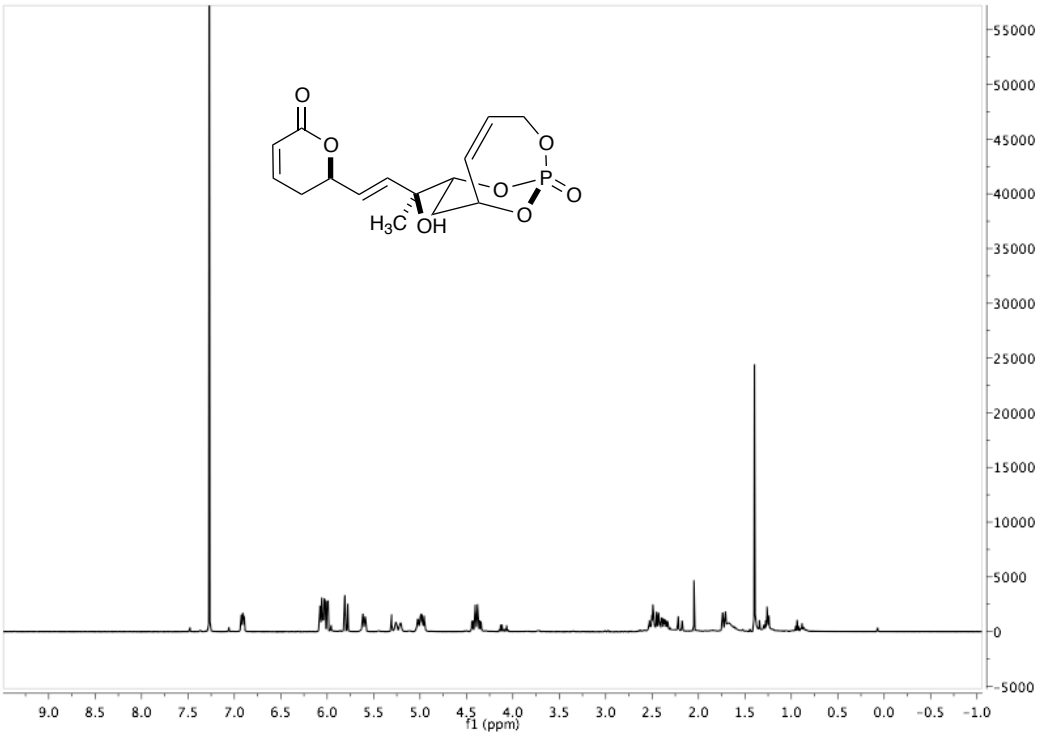
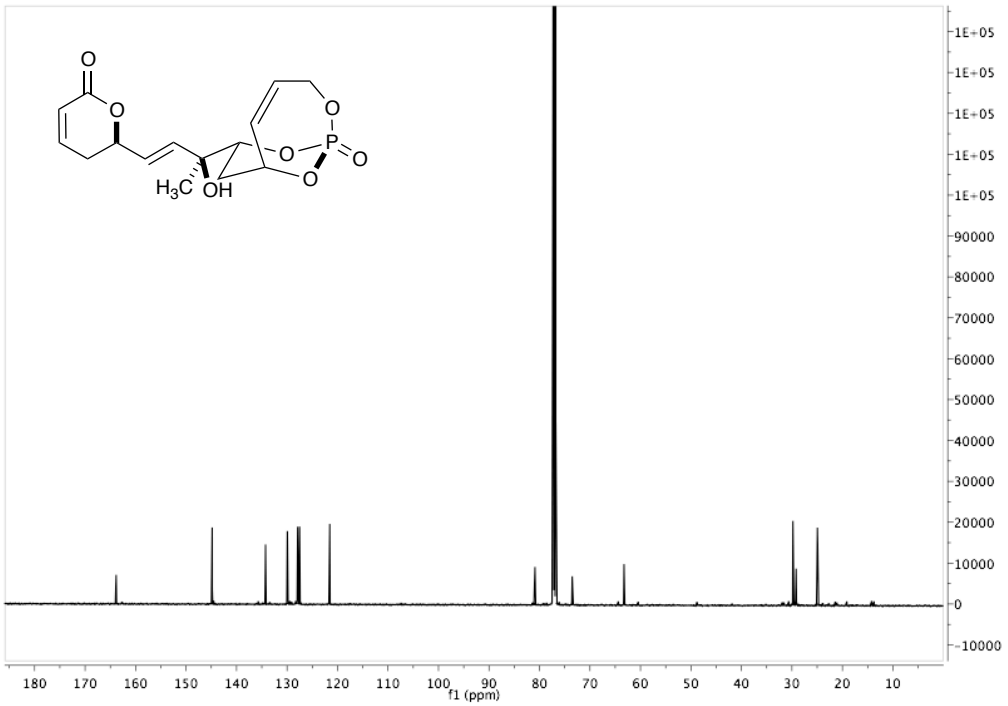
f1 (ppm)

(*R*)-6-((*S*,*E*)-3-hydroxy-3-((1*S*,6*R*,8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (2.157)

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OH
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1E+05
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80000
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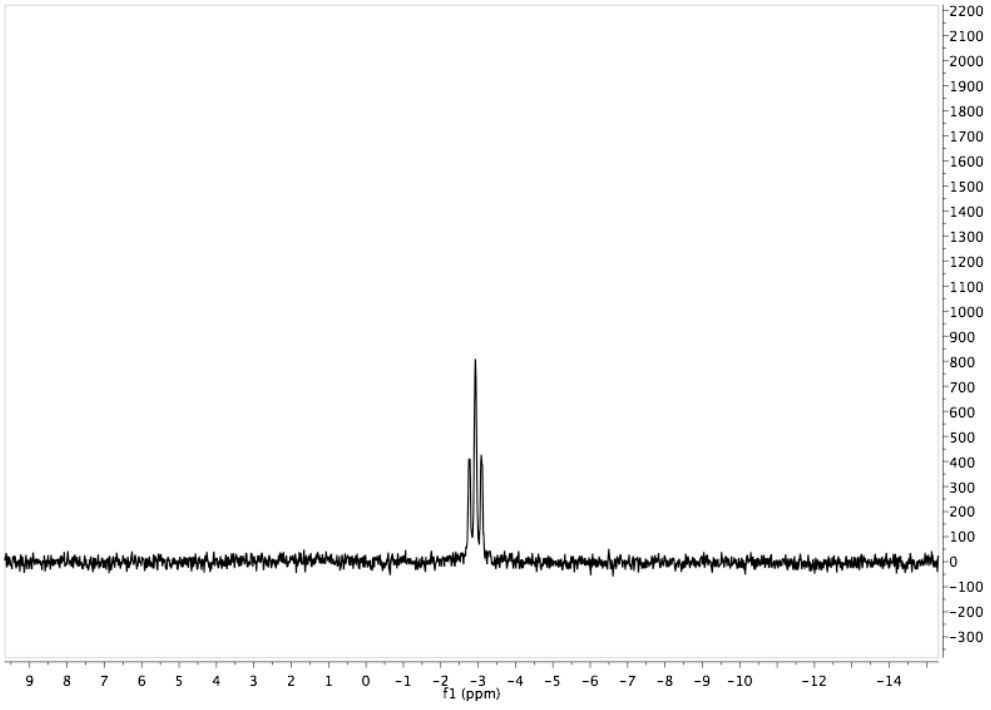
f1 (ppm)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1900
1800
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1500
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1300
1200
1100
1000
900
800
700
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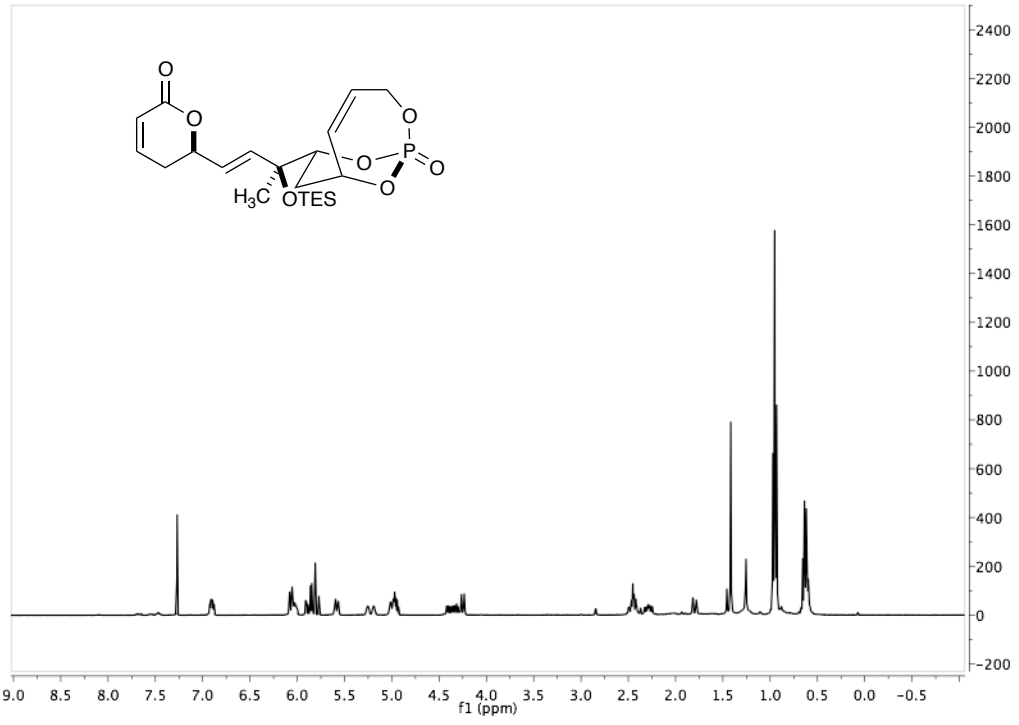
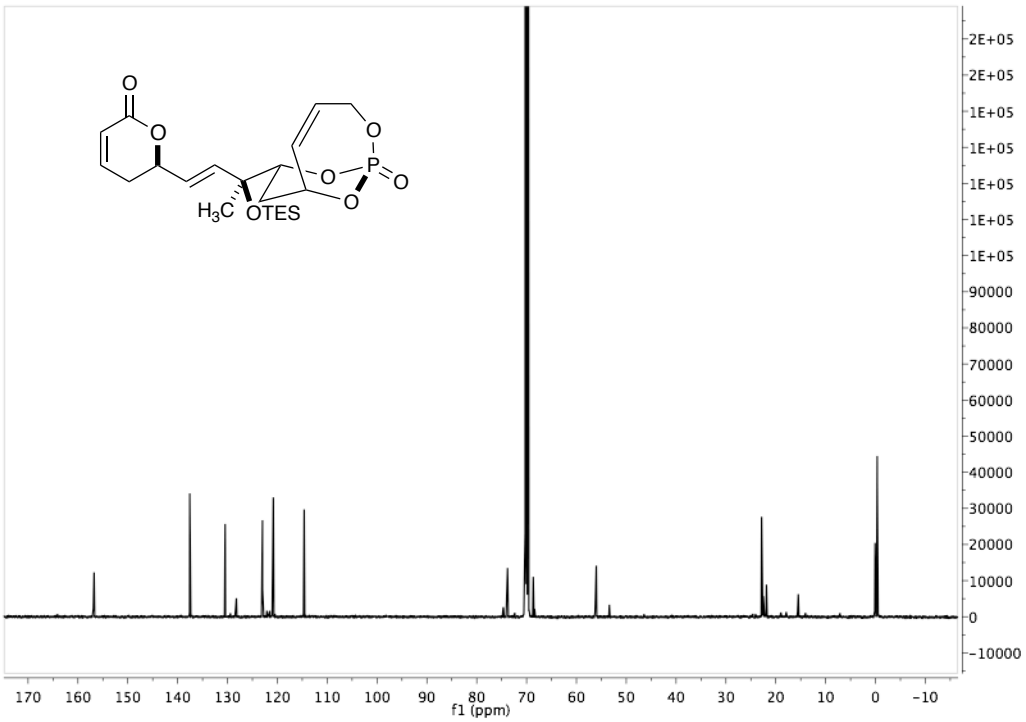
400
300
200
100
0
-100
-200
-300
9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -12 -14
f1 (ppm)

(*R*)-6-((*S*,*E*)-3-((1*S*,6*R*,8*R*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)-3-((triethylsilyl)oxy)but-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one(TES-2.157).

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P
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2E+05
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1E+05
1E+05
90000
80000
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20000
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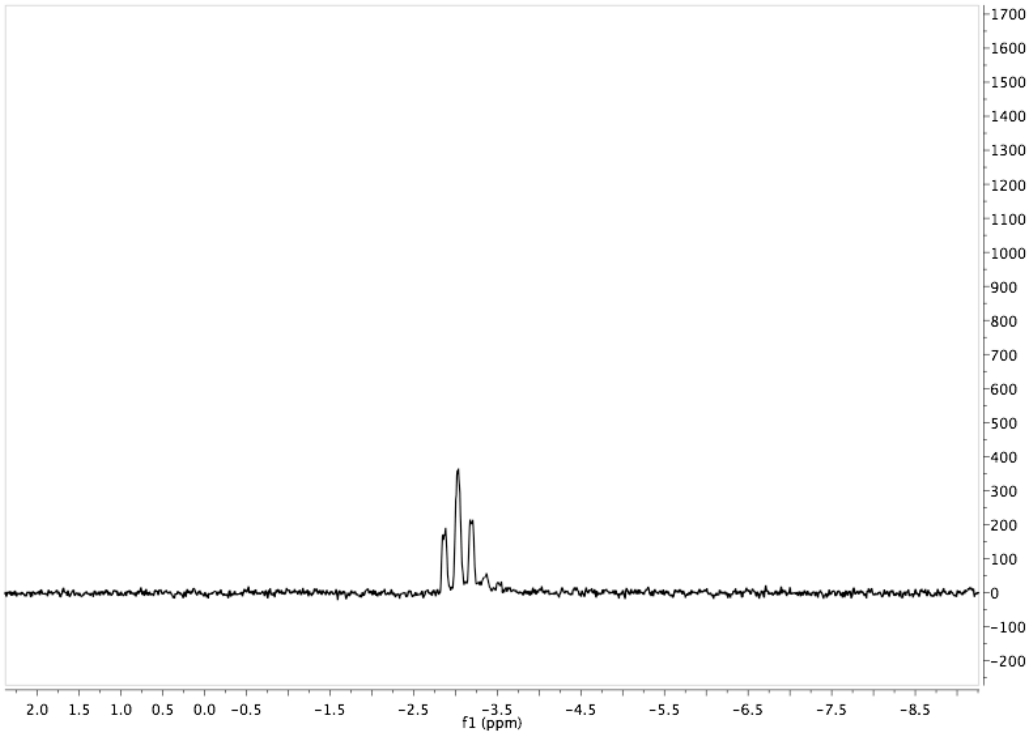
f1 (ppm)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200
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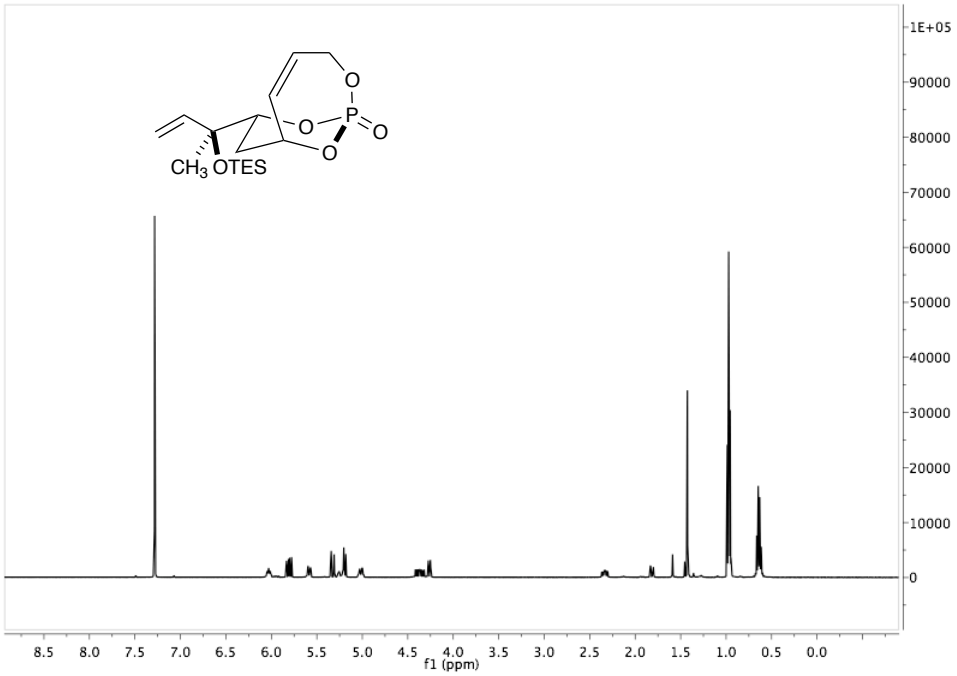
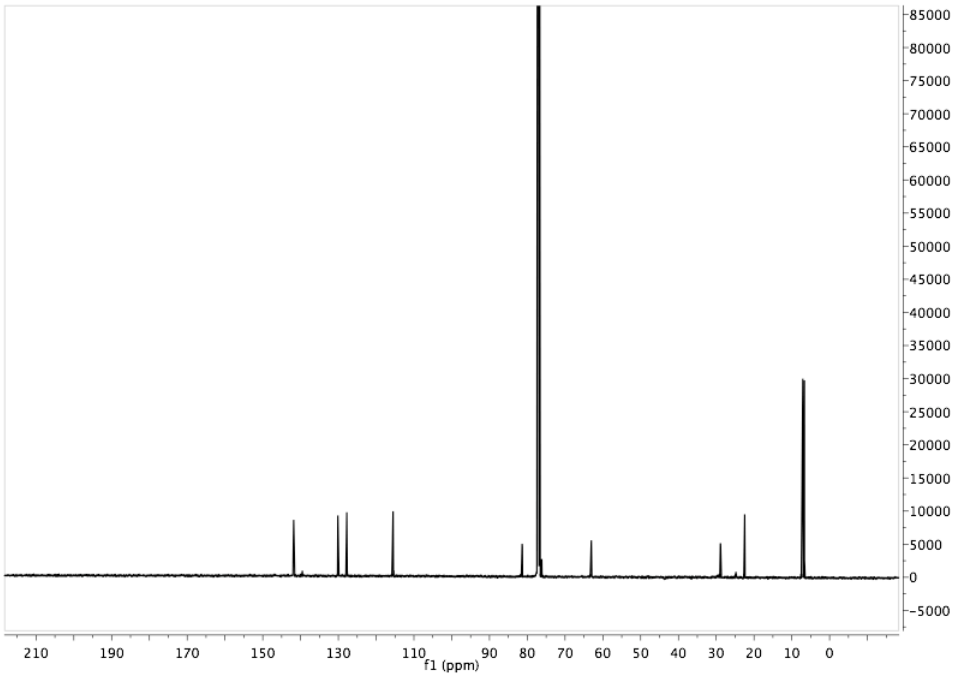
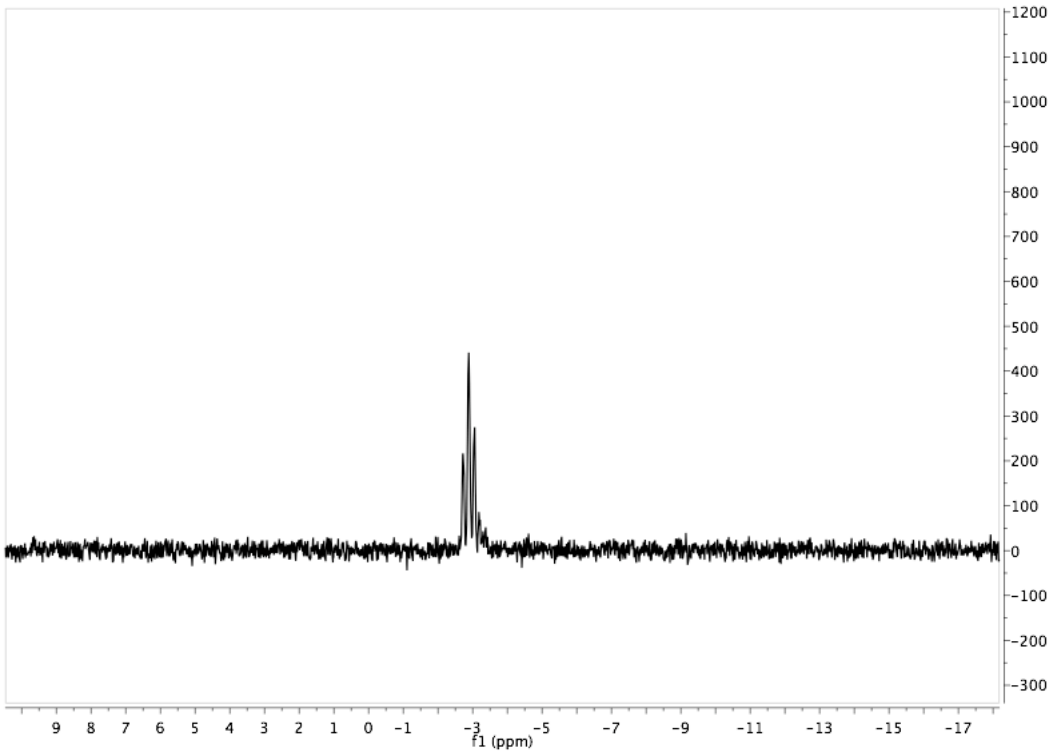
0
-100
-200
2.0 1.5 1.0 0.5 0.0 -0.5 -1.5 -2.5 -3.5 -4.5 -5.5 -6.5 -7.5 -8.5
f1 (ppm)

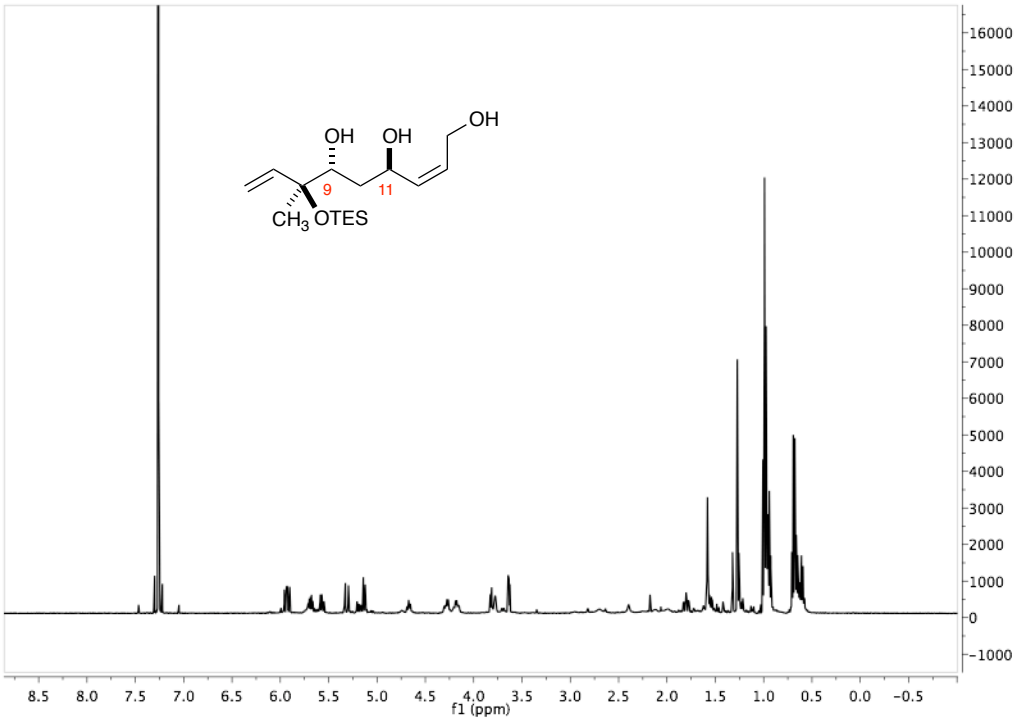
(1*S*,6*R*,8*R*)-8-((*R*)-2-((triethylsilyl)oxy)but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene1-oxide(2.153)

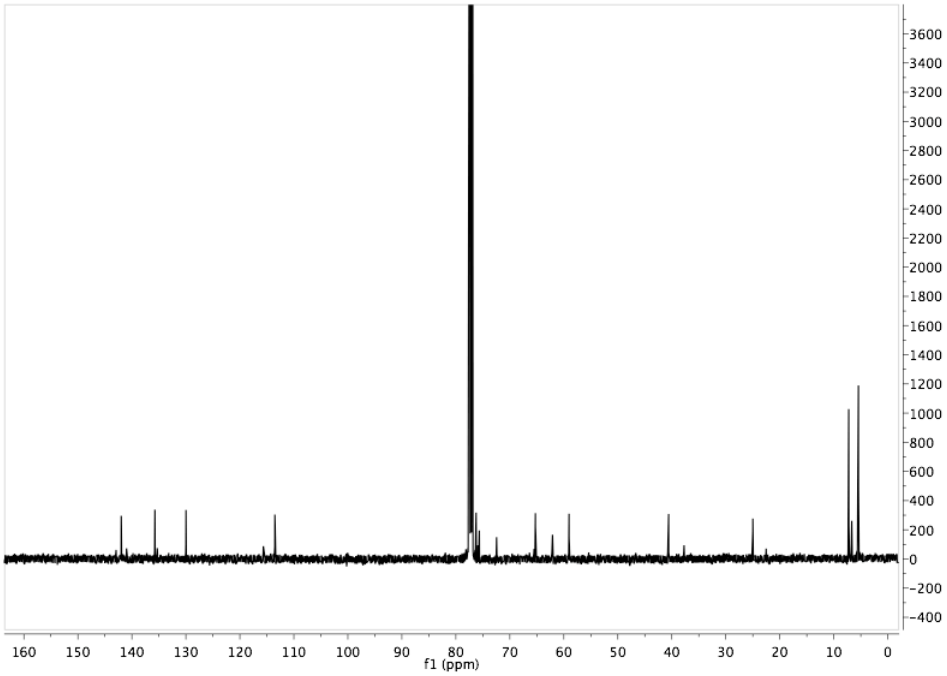




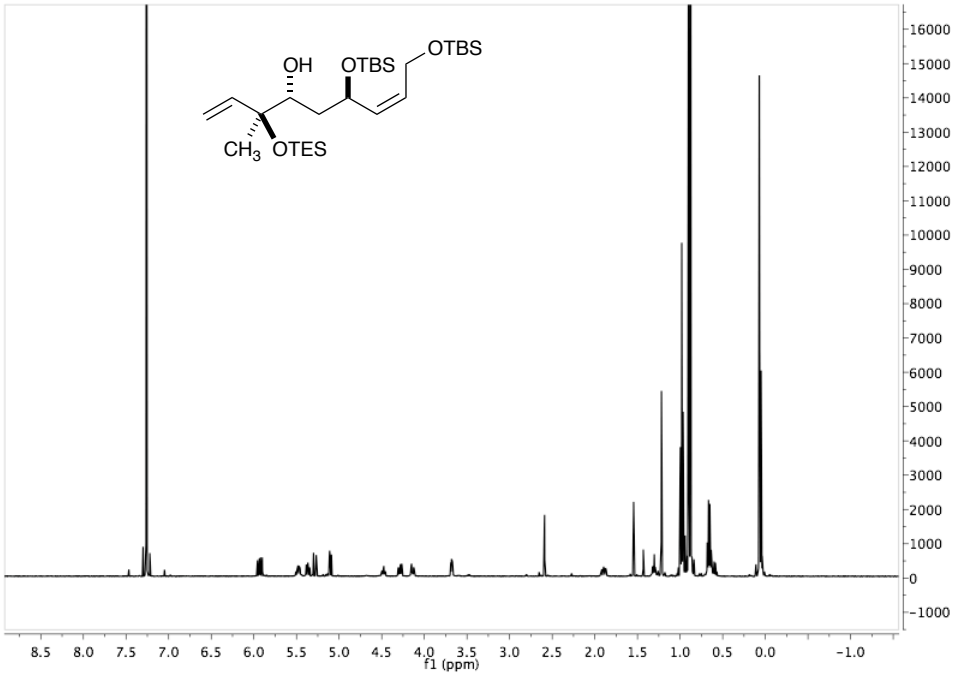

1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
−200
−300
9 8 7 6 5 4 3 2 1 0 −1 −3 −5 −7 −9 −11 −13 −15 −17
f1 (ppm)

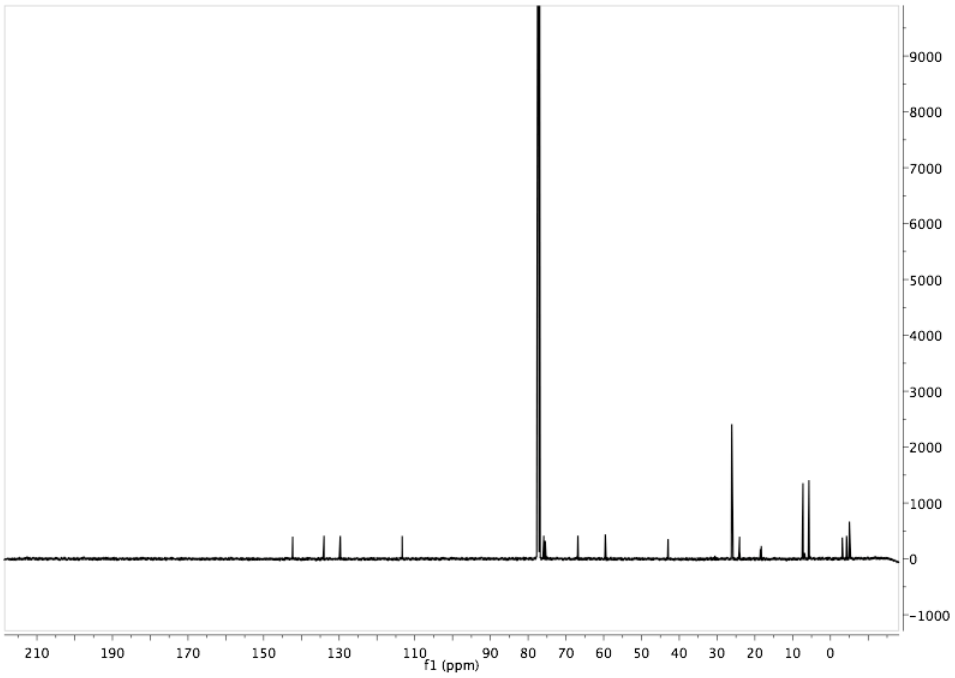
(4*R*,6*R*,7*R*,*Z*)-7-methyl-7-((triethylsilyl)oxy)nona-2,8-diene-1,4,6-triol (1.41).



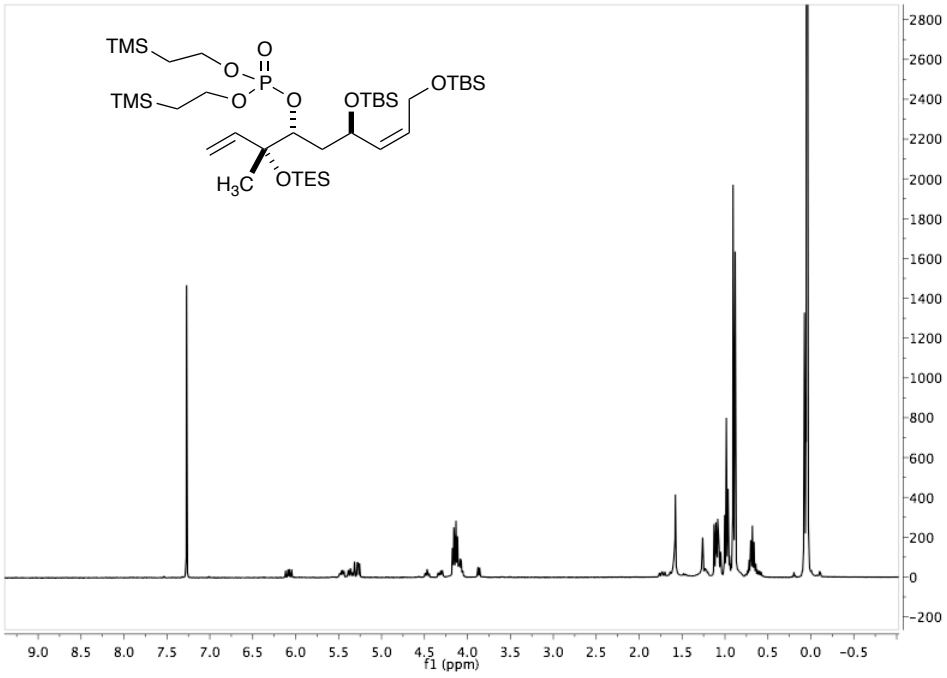


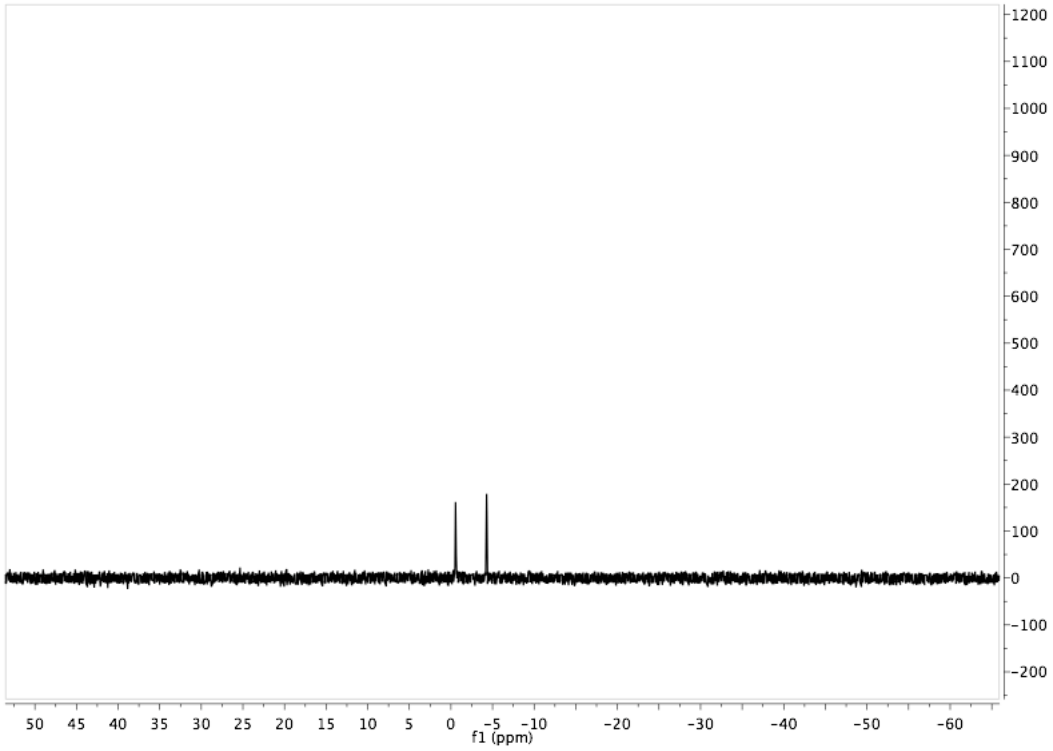
(5*S*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol (2.160)





(5*R*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5,13,13,14,14-pentamethyl-5-vinyl-4,12-dioxa-3,13-disilapentadec-9-en-6-yl-bis(2-(trimethylsilyl)ethyl) phosphate (2.161)

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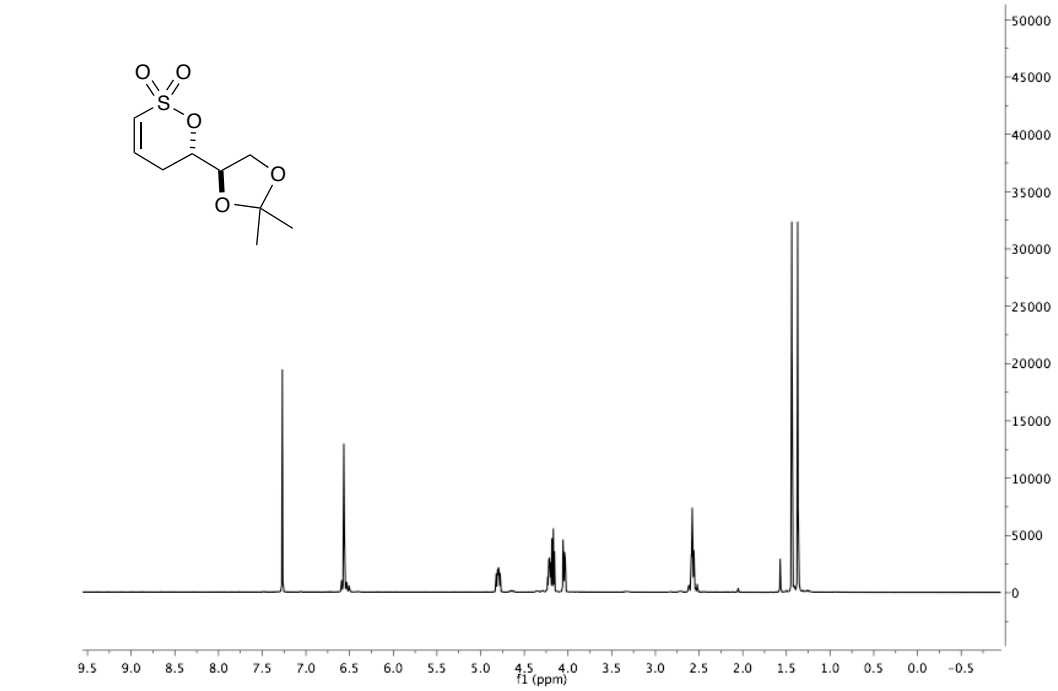
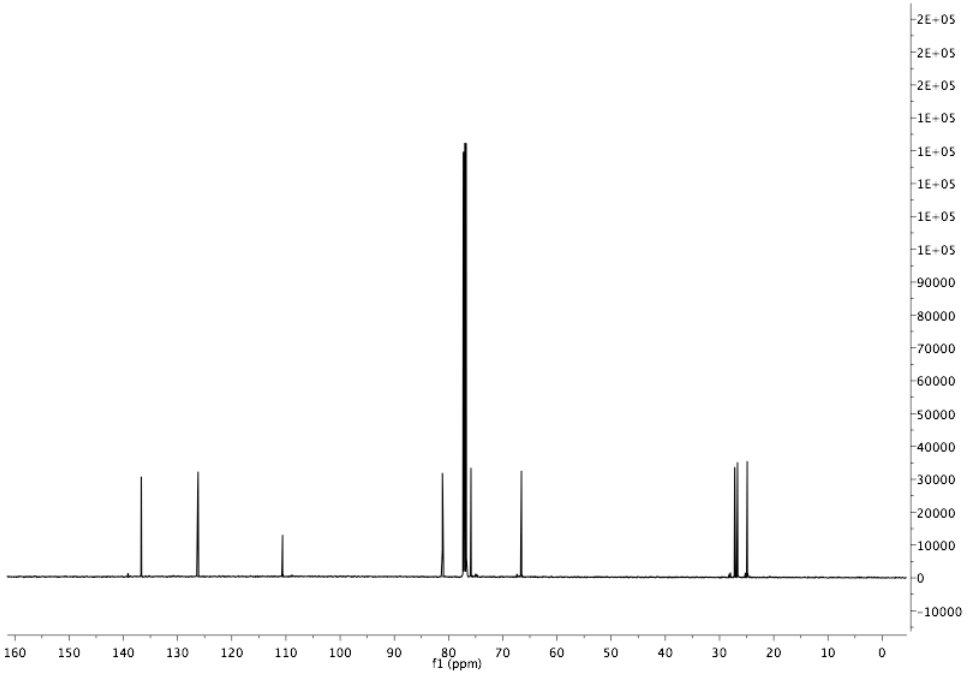
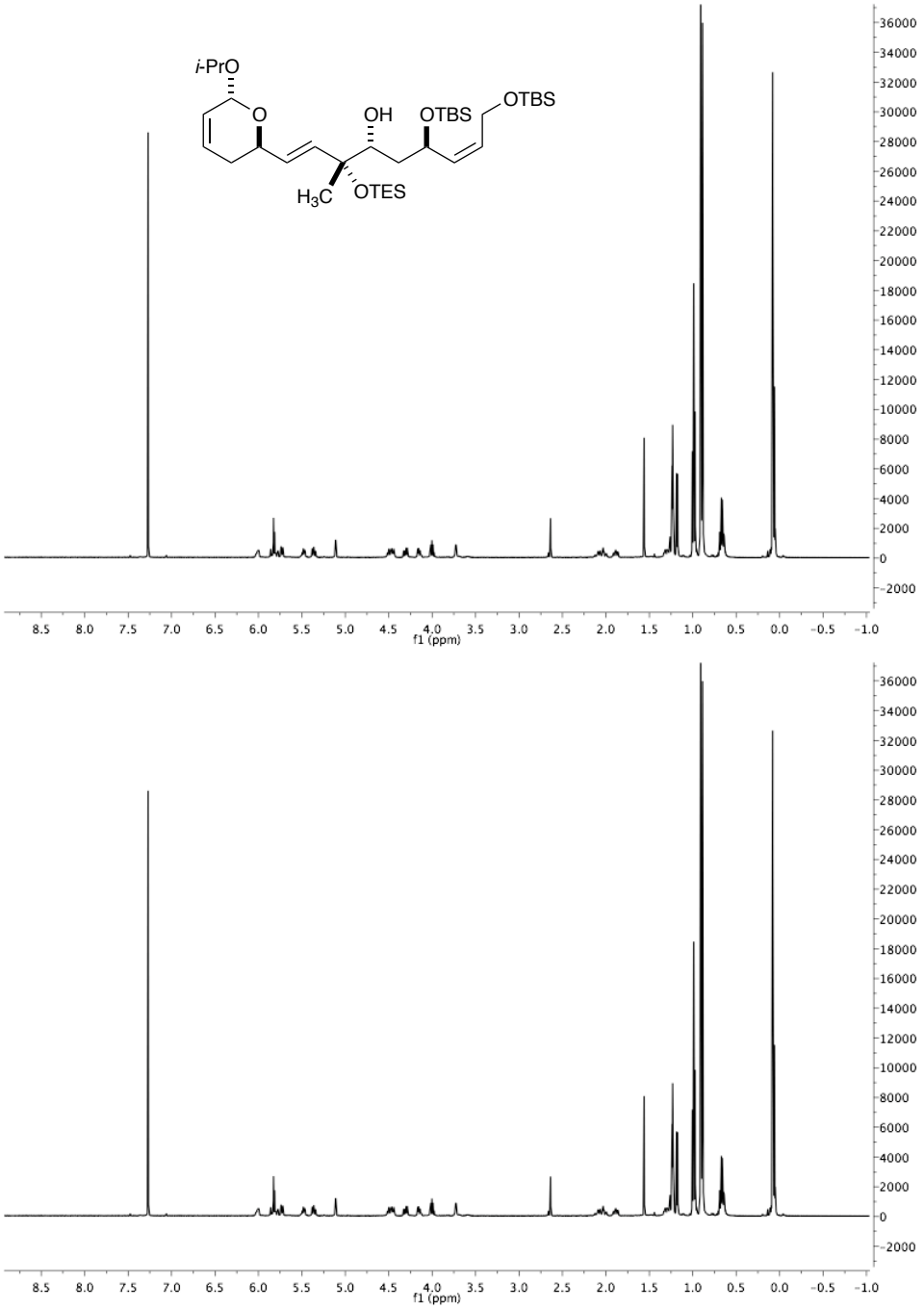
-100
-200
50 45 40 35 30 25 20 15 10 5 0 -5 -10 -20 -30 -40 -50 -60
f1 (ppm)

(*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-1,2-oxathiine 2,2-dioxide (2.165).





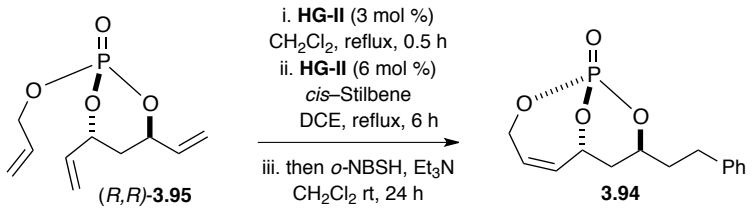
(5*R*,6*R*,8*R*,*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-3,3-diethyl-5-((*E*)-2-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)vinyl)-5,13,13,14,14-pentamethyl-4,12-dioxa-3,13-disilapentadec-9-en-6-ol (TBS-2.158)



General Experimental Methods

All reactions were carried out in an oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, THF and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3 (Grubbs, R. H.; Rosen. R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). Et_3N was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. ^{31}P NMR spectra was recorded on Bruker DRX-400 spectrometer operating at 162 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

(1*R*,6*R*,8*S*)-8-phenethyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (3.94)



To a stirring solution of triene (*R*,*R*)-**3.95**[1] (125 mg, 0.543 mmol) in freshly distilled, freeze-degas-thawed CH_2Cl_2 (78 mL, 0.007 M) was added Hoveyda-Grubbs 2nd Gen.(HG–II) catalyst (13.6 mg, 0.022 mmol) and the reaction was refluxed for 45 min. After completion of RCM, *cis*–stilbene [2 equiv with respect to the triene (*R*,*R*)-**3.95** was dissolved in freshly distilled, freeze-degas-thawed 1,2-dichloroethane (11 mL, 0.05 M) and added to the crude reaction mixture, followed by addition of HG–II (20 mg, 0.033 mmol). The reaction was continued at 70 ºC with simultaneous evaporation of the excess CH_2Cl_2 from the previous reaction to reach optimal concentration for CM reaction (11 mL, 0.05 M). The reaction was continued (at 70 ºC) for an additional 6 h until all the starting materials were consumed by TLC analysis. The reaction mixture was cooled to room temperature and *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (1.4 g, 5.43 mmol) and Et_3N (2.6 mL, at 2 mL/g of *o*-NBSH) were added, upon which the reaction was stirred at RT for 10 h. (**Note**: The reaction flask was wrapped with aluminum foil to avoid decomposition of *o*-NBSH due to light). Excess *o*-NBSH (676 mg, 2.7mmol) and Et_3N (1.3 mL, at 2 mL/g of *o*-NBSH) were added and the reaction was stirred for an additional 5 h. The reaction mixture was diluted with EtOAc (20 mL) and extracted with sat. $NaHCO_3$ (15 mL). The aqueous layer was washed with EtOAc (2x10) and the

combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure. Purification by flash column chromatography (1:1 hexanes/EtOAc) afforded 81 mg of desired product **3.94** (52% overall yield) as a colorless solid.

R_f = 0.25 (1:3 Hexanes/EtOAc);

M.P:110–112 ºC;

FTIR (thin film): 3026, 2852, 2923, 1454, 1296 cm^{-1};

Optical Rotation: $[\alpha]_D$ = -89.6 (*c* = 0.895, $CHCl_3$);

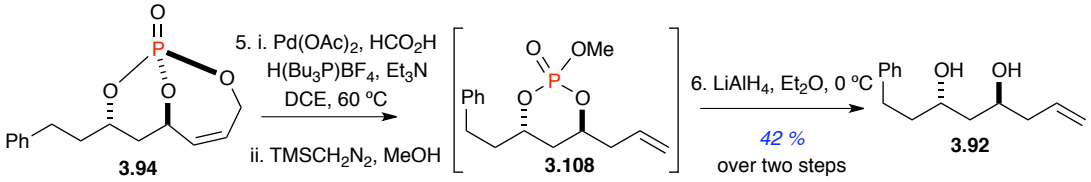
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.26 (m, 2H), 7.23–7.17 (m, 3H), 6.04–5.97 (m, 1H), 5.58 (ddd, *J* = 11.8, 3.8, 2.3 Hz, 1H), 5.19 (br.d, J_{PH} = 24.6 Hz, 1H), 5.01 (dddd, *J*= 11.8, 7.5, 5.4, 2.8 Hz, 1H), 4.60 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.36 (ddd, *J* = 27.7, 14.8, 6.7 Hz, 1H), 2.91–2.82 (m, 1H), 2.77–2.68 (m, 1H), 2.27–2.17 (m, 1H), 2.07 (ddd, *J* = 14.1, 9.1, 4.6 Hz, 1H), 1.91–1.79 (m, 1H), 1.72–1.63 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 140.8, 129.8, 129.0 (2C), 128.0 (2C), 127.9, 126.1, 77.2 (d, J_{CP} = 6.7 Hz), 75.8 (d, J_{CP} = 6.7 Hz), 63.0 (d, J_{CP} = 6.4 Hz), 37.5 (d, J_{CP} = 9.3 Hz), 34.8 (d, J_{CP} = 5.9 Hz), 30.7 ;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.98;

HRMS cald for $C_{14}H_{17}O_4PNa$ $(M+Na)^+$ 303.0762; found 303.0764 (TOF MS ES+).

(3*S*,5*S*)-1-phenyloct-7-ene-3,5-diol (3.92)



To a stirring solution of phosphate **3.94** (30 mg, 0.105 mmol) in 0.4 mL of DCE were added Et_3N (0.07 mL, 4.9 mmol) and HCOOH (0.0095 mL, 2.48 mmol). The solution of 5 mol % $Pd(OAc)_2$ (1.5 mg, 0.007 mmol) and $H(Bu_3P)BF_4$ (1.8 mg, 0. 007 mmol) in 0.2 mL of DCE was quickly cannulated into the reaction mixture containing phosphate. The reaction was heated to 60 ºC and stirred at this temperature until the color of the reaction turned black (~1 h) as well as disappearance of starting material by TLC analysis. The reaction was cooled to room temperature, diluted with 2 mL CH_2Cl_2 and 1 mL of 10% aqueous HCl was added. The layers were separated and the aqueous layer was re-extracted (2 x 3 mL) with CH_2Cl_2. The organic layer was then concentrated to ~1 mL under reduced pressure MeOH (0.2 mL) followed by $TMSCHN_2$ (0.3 mL, 2.0M in diethyl ether) were added to the stirring solution that caused the reaction to bubble vigorously. The reaction was allowed to stir for 5 min. and was monitored for disappearance of the phosphate acid. Upon completion of the reaction, a drop of glacial acetic acid was added and the mixture was extracted with CH_2Cl_2 and a saturated $NaHCO_3$ (aq) solution. The aqueous layer was re-extracted (2 x 3mL) with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the crude mixture was subjected to the next reaction with out purification.

The 1:1 diastereomeric phosphate **3.108** in Et_2O (3.7mL) was cooled to 0 ºC and $LiAlH_4$ (7.9 mg, 0.21 mmol) was added slowly. Upon completion of the addition, the reaction was stirred at 0 ºC for 1 h, and quenched via slow sequential addition of H_2O (8 μL), 10% NaOH (8 μL),and H_2O (24 μL), and the reaction was removed from the ice bath. After stirring for 1 h, white salts formed, and the salts were filtered through a pad of Celite® and washed with Et_2O and filtrate was concentrated under reduced pressure. The resulting clear oil was passed through a short silica plug (2:1 Hexane/EtOAc) afforded 10 mg of **3.92** in 42% overall yield as a colorless oil.

R_f = 0.25 (2:1 Hexanes/EtOAc);

FTIR (neat) 3018, 2927, 2956, 2854, 1274, 1215, 742 cm^{-1};

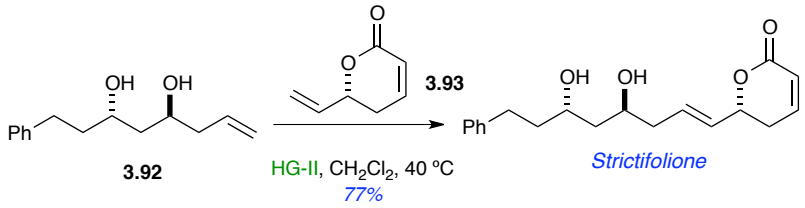
Optical Rotation: $[\alpha]_D$ = +4.2 (*c* = 0.95, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31–7.27 (m, 2H), 7.23–7.18 (m, 3H), 5.86–5.76 (m, 1H), 5.17 (s, 1H), 5.15–5.13 (m, 1H), 4.04–3.96 (m, 2H), 2.81 (ddd, *J* = 13.8, 10.0, 5.7 Hz, 1H), 2.68 (ddd, *J* = 13.8, 9.8, 6.5 Hz, 1H), 2.55 (s, OH), 2.37 (s, OH), 2.30–2.5 (m, 2H), 1.92–1.84 (m, 1H), 1.83–1.74 (m, 1H), 1.70–1.66 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.0, 134.5, 128.4 (3C), 125.9 (2C), 118.4, 68.8, 68.2, 42.0, 42.0, 39.1, 32.2;

HRMS cald. for $C_{14}H_{20}O_2Na$ $(M+Na)^+$ 243.1361; found 243.1359 (TOF MS ES+)

(*R*)-6-((4*S*,6*S*,*E*)-4,6-dihydroxy-8-phenyloct-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one– (+)-Strictifolione (3.1).



To a stirring solution of olefin **3.92** (8.4 mg, 0.038 mmol, 2 equiv.) in degassed CH_2Cl_2 (0.7 mL, 0.05M) was added lactone **3.93** (2.5 mg, 0.02 mmol) and HG–II catalyst (1.2 mg, 0.002 mmol, 5 mol %) and the reaction was refluxed at 40 ºC for 1.5 h until all starting material were consumed. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. Purification by flash column chromatography (2:1 Hexane/EtOAC) afforded **3.1** (4.8 mg, 77% yield) as a white crystalline solid.

R_f = 0.3 (2:1 Hexanes/EtOAc);

M.P: 111–113 ºC;

FTIR (neat) 3415, 3026, 2921, 2850, 2356, 1712, 771 cm^{-1};

Optical Rotation: $[\alpha]_D$ = +78.8 (*c* = 0.085, $CHCl_3$);

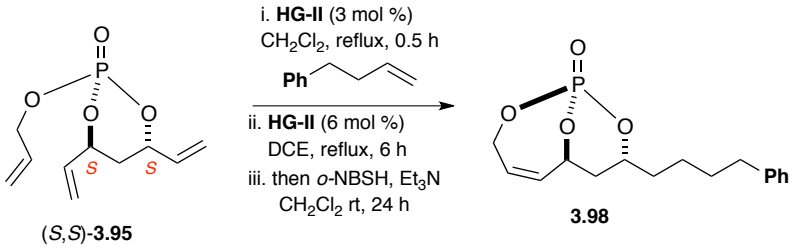
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.27 (m, 2H), 7.23–7.19 (m, 3H), 6.90 (ddd, *J* = 9.7, 5.1, 3.6 Hz, 1H), 6.05 (ddd, *J* = 9.8, 2.1, 1.8 Hz, 1H), 5.87 (ddd, *J* = 14.68, 7.6, 7.05 Hz, 1H), 5.70 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.95–4.86 (m, 1H), 3.99–4.03 (m, 2H),

2.87–2.62 (m, 2H), 2.44 (m, 2H), 2.30 (t, J = 6.6 Hz, 2H), 1.93–1.74 (m, 2H), 1.67 (t, J = 5.6 Hz, 2H), 1.57 (s, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 163.9, 144.6, 141.8, 131.0 , 130.1, 128.5 (2 C), 128.4 (2C), 125.9, 121.6, 77.7, 68.9, 68.3, 42.1, 40.4, 39.0, 32.2, 29.7;

HRMS cald. for $C_{19}H_{24}O_4Na$ $(M+Na)^+$ 339.1572; found 339.1584 (TOF MS ES+)

(1*S*,6*S*,8*R*)-8-(4-phenylbutyl)-2,9,10-trioxa-1phosphabicyclo[4.3.1]dec-4-ene 1-oxide (3.98)



To a stirring solution of triene (*S*,*S*)-**3.95**[1] (50 mg, 0.217 mmol) in freshly distilled, freeze-degas-thawed CH_2Cl_2 (31 mL, 0.007 M) was added HG–II (5.4 mg, 0.0087mmol) and the reaction was refluxed for 45 min. After completion of RCM, but-3-en-1-ylbenzene [0.065 mL, 0.434 mmol] was dissolved in freshly distilled, freeze-degas-thawed 1,2-dichloroethane (4.3 mL, 0.05 M) and added to the crude reaction mixture, followed by addition of HG–II catalyst (8.1 mg, 0.013 mmol). The reaction was continued at 70 ºC with simultaneous evaporation of the excess CH_2Cl_2 from the previous reaction to reach optimal concentration for CM reaction (4.3 mL, 0.05 M). The reaction was continued (at 70 ºC) for an additional 6 h until all the starting materials were consumed by TLC analysis. The reaction mixture was cooled to room temperature and *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH) (540.3 mg, 2.17 mmol) and Et_3N (1.1 mL, at 2 mL/g of *o*-NBSH) were added, upon which the reaction was stirred at RT 10 h. (**Note**: The reaction flask was wrapped with aluminum foil to avoid decomposition of *o*-NBSH due to light). Excess *o*-NBSH (174.3 mg, 0.7mmol) and Et_3N (0.55 mL, at 2 mL/g of *o*-NBSH) were added and the reaction was stirred for an additional 5 h. The reaction

mixture was diluted with EtOAc (10 mL) and extracted with sat. $NaHCO_3$ (5 mL). The aqueous layer was washed with EtOAc (2 x 5 mL) and the combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure. Purification by flash column chromatography (1:1 hexanes/EtOAc) afforded 36 mg of desired product **3.98** (54 % overall yield) as a white solid.

R_f = 0.26 (1:2 Hexanes/EtOAc);

M.P: 90–92 ºC;

FTIR (thin film): 3024, 2929, 2856, 1452, 1298, 1068,972 cm^{-1};

Optical Rotation: $[\alpha]_D$ = +65.45 (*c* = 0.165, $CHCl_3$);

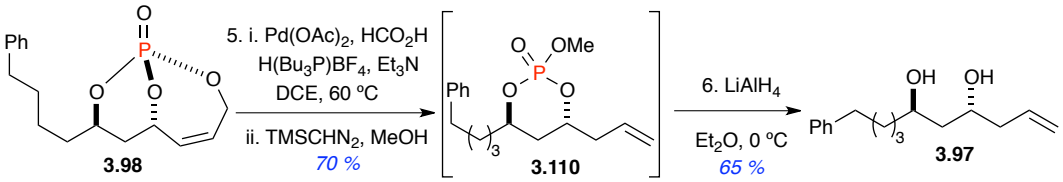
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31–7.27 (m, 3H), 7.23–7.15 (m, 2H), 6.03 (dddd, *J* =11.9, 6.7, 3.0, 2.2 Hz, 1H), 5.58 (ddd, *J* = 11.8, 3.8, 2.3 Hz, 1H), 5.19 (br.d, J_{PH} = 24.6 Hz, 1H), 5.01 (dddd *J* = 17.4, 12.1, 6.1, 2.8 Hz, 1H), 4.60 (m, 1H), 4.36 (ddd, *J* = 27.7, 14.8, 6.7 Hz, 1H), 2.6 (t, *J* = 7.6 Hz, 2H), 2.17 (ddd, *J* =14.6, 11.9, 6.2 Hz 1H), 1.80 (ddd, *J* = 18.7, 8.4, 5.4 Hz, 1H), 1.72–1.51 (m, 4H), 1.46–1.38 (m, 1H) 1.26 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.2, 129.7, 128.4 (2C), 128.3 (2C), 128.0, 125.8, 77.1, 76.6 (d, J_{CP} = 6.8 Hz), 62.9 (d, J_{CP} = 6.3 Hz), 35.7, 37.6 (d, J_{CP} = 9.3 Hz), 34.8 (d, J_{CP} = 5.9 Hz), 31.0, 24.2;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -3.06;

HRMS cald for $C_{16}H_{21}O_4PNa$ $(M+Na)^+$ 331.1075; found 331.1074 (TOF MS ES+).

(4*R*,6*R*)-10-phenyldec-1-ene-4,6-diol (3.97)



To a stirring solution of phosphate **3.98** (145 mg, 0.473 mmol) in 1.9 mL of DCE were added Et_3N (0.3 mL, 2.1 mmol) and HCOOH or formic acid (0.041 mL, 1.06 mmol). The solution of 5 mol % $Pd(OAc)_2$ (6.4 mg, 0.028 mmol) and $H(Bu_3P)BF_4$ (8.09 mg, 0.028 mmol) in 0.9 mL of DCE was quickly cannulated in to the reaction mixture containing phosphate. The reaction was heated to 60 ºC and stirred at this temperature until the color of the reaction turned black (~1 h) as well as disappearance of starting material by TLC analysis.

The reaction was cooled to room temperature, diluted with 2 mL CH_2Cl_2 and 1.5 mL of 10% aqueous HCl was added. The layers were separated and the aqueous layer was re-extracted (2x 5 mL) with CH_2Cl_2. The organic layer was then concentrated to ~1 mL under reduced pressure. MeOH (0.3 mL) followed by $TMSCHN_2$ (0.3 mL, 2.0M in diethyl ether) were added to the stirring solution that caused the reaction to bubble vigorously. The reaction was allowed to stir for 5 min. and was monitored for disappearance of the phosphate acid. Upon completion of the reaction a drop of glacial acetic acid was added and the mixture was extracted with CH_2Cl_2 and a saturated solution of $NaHCO_3$. The aqueous layer was re-extracted (2x 5 mL) with CH_2Cl_2, dried (Na_2SO_4),

filtered, and concentrated under reduced pressure. Flash chromatography (2:1 Hexane/EtOAC) provided 100 mg of **3.110** (~1:1 diastereomeric mixture at phosphate) in 70% yield as a clear oil.

The 1:1 diastereomeric phosphate mixture (100 mg, 0.328 mmol) in Et_2O (11 mL) was cooled to 0 ºC and $LiAlH_4$ (24.8 mg, 0.656 mmol) was slowly added. Upon completion of the addition, the reaction was stirred at 0 ºC for 1 h, and quenched via slow sequential addition of H_2O (25 μL), 10% NaOH (25 μL), and H_2O (75 μL), and warmed to RT. After stirring at RT for 1 h, white salts formed, the salts were filtered through a pad of Celite® and washed with Et_2O and was concentrated under reduced pressure. The resulting clear oil was passed through a short silica plug (1:2 Hexane/EtOAc) to afford 53 mg of **3.97** in 65% yield as a colorless oil.

R_f = 0.2 (1:3 Hexanes/EtOAc);

FTIR (neat) 3361, 3076, 3026, 2931, 2856, 1641, 1452, 1064, 698 cm^{-1};

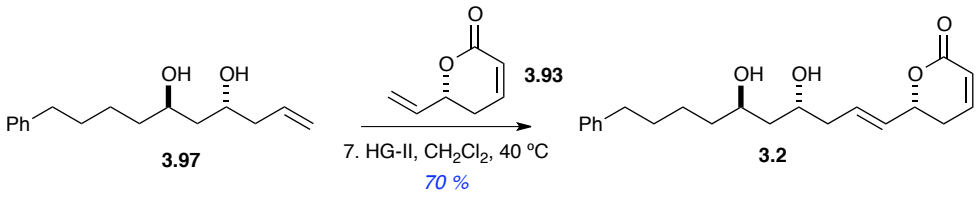
Optical Rotation: $[\alpha]_D$ = -5.37 (*c* = 0.67, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31–7.26 (m, 2H), 7.16–7.21 (m, 3H), 5.86–5.77 (m, 1H), 5.17 (m, 1H), 5.14 (m, 1H), 4.03–3.92 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.38 (s, 2 OH), 2.30–2.25 (m, 2H), 1.69–1.25 (m, 8H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.5, 134.6, 128.3 (2C), 128.3 (2C), 125.7, 118.3, 69.2, 68.2, 42.0, 41.8, 37.3, 35.9, 31.4, 25.4;

HRMS cald. for $C_{16}H_{24}O_2Na$ $(M+Na)^+$ 271.1674; found 271.1672 (TOF MS ES+)

(*R*)-6-((4*R*,6*R*,*E*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (3.2).



To stirring solution of olefin **3.97** (14 mg, 0.056 mmol, 2 equiv.) in degassed CH_2Cl_2 (1.1 mL, 0.05M was added lactone **3.93** (3.49 mg, 0.02 mmol) and HG–II catalyst (1.8 mg, 0.002 mmol, 5 mol %) and refluxed for 1.5 h. The reaction was cooled to RT, and solvent was removed under reduced pressure. Purification by flash chromatography (2:1 Hexane/EtOAC) provided **3.2** (6.8 mg, 70% yield) as a colorless liquid.

R_f = 0.3 (1:4 Hexanes/EtOAc);

FTIR (neat) 3415, 3026, 2921, 2854, 2356, 1708, 1248 cm^{-1};

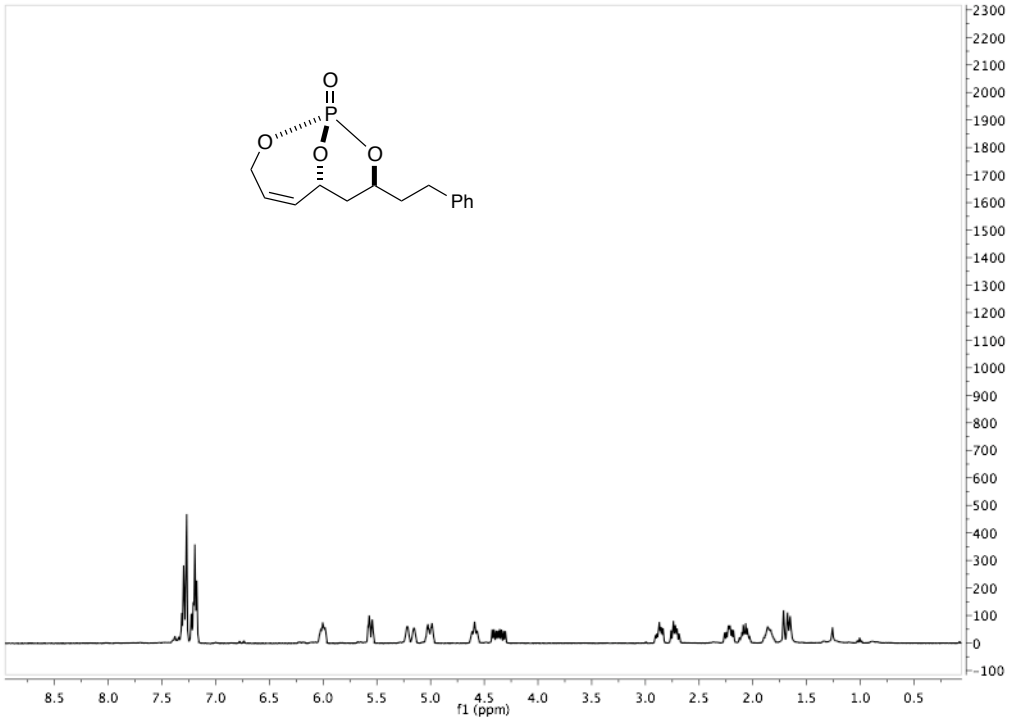
Optical Rotation: $[\alpha]_D$ = +62 (*c* = 0.190, $CHCl_3$);

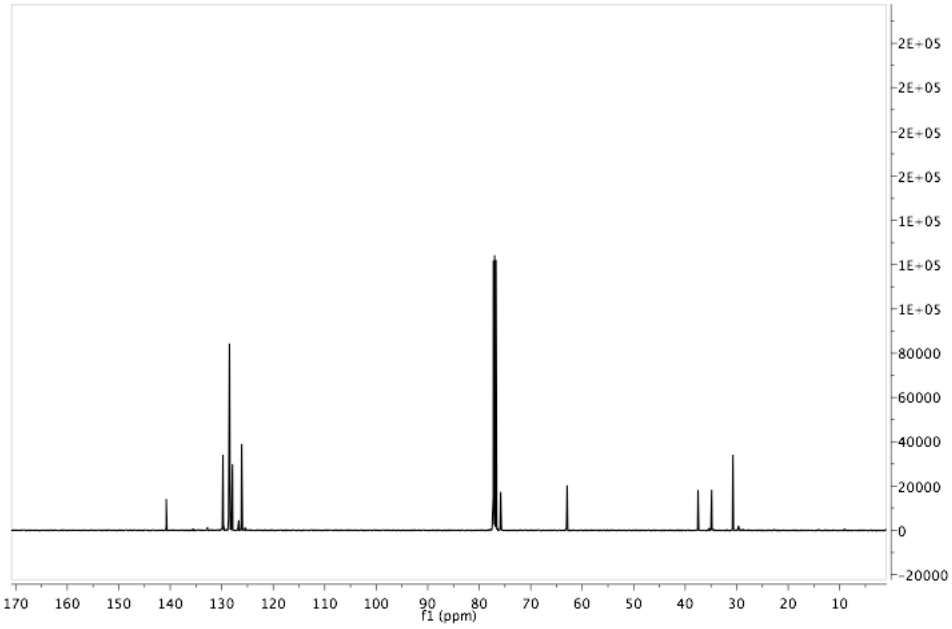
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.27 (m, 2H), 7.23–7.19 (m, 3H), 6.90 (ddd, *J* = 8.6, 4.6, 3.9 Hz, 1H), 6.05 (dt, *J* = 9.7, 1.6 Hz, 1H), 5.87 (ddd, *J* = 14.68, 7.9, 6.72 Hz, 1H), 5.70 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.91 (dd, *J* = 14.6, 6.5 Hz, 1H), 4.04–3.99 (m, 1H), 3.94 (td, *J* = 7.6, 3.9 Hz, 1H), 2.63 (t, 2H), 2.46–2.43 (m, 2H), 2.30 (t, *J* = 6.7 Hz, 2H), 1.71–1.55 (m, 6H), 1.53–1.44 (m, 2H), 1.36 (ddd, *J* = 12.2, 7.1, 4.4 Hz, 1H), 1.26 (s, 1H);

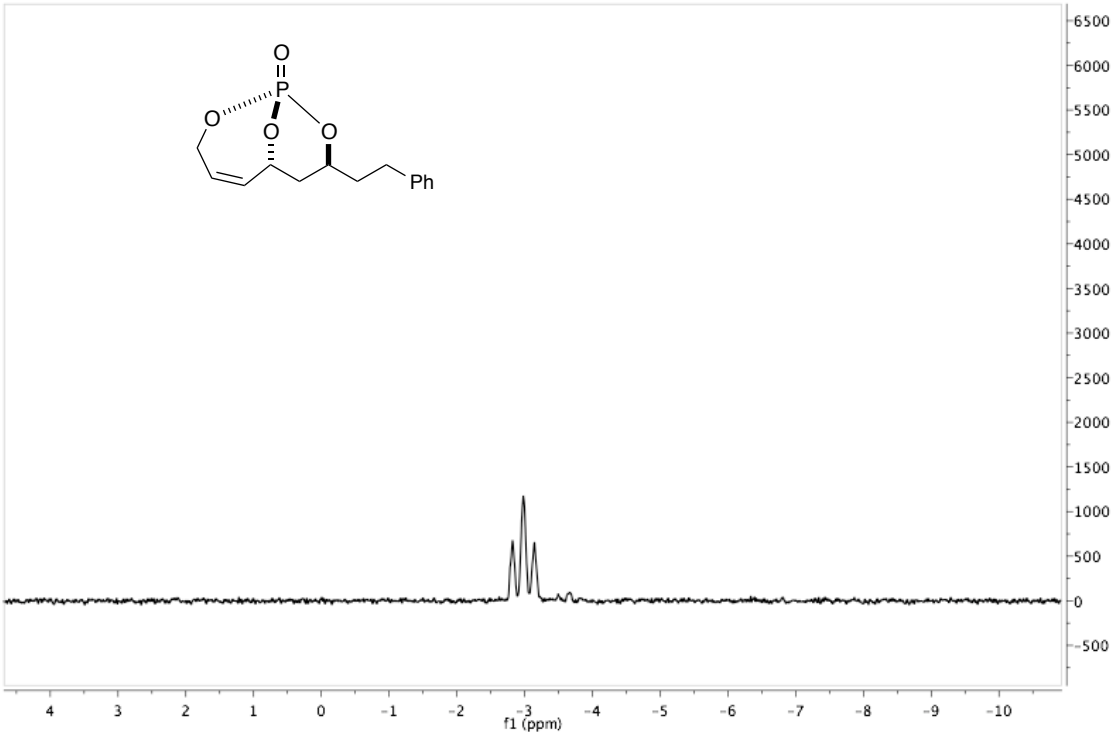
^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 164.0, 144.7, 142.5, 131.2, 130.0, 128.4 (2C), 128.3 (2C), 125.7, 121.6, 77.8, 69.2, 68.2, 41.9, 40.3, 37.3, 35.8, 31.4, 29.7, 25.4;

HRMS cald. for $C_{21}H_{28}O_4Na$ $(M+Na)^+$ 367.1885; found 367.1876 (TOF MS ES+)

(1*R*,6*R*,8*S*)-8-phenethyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene-1-oxide (3.94)



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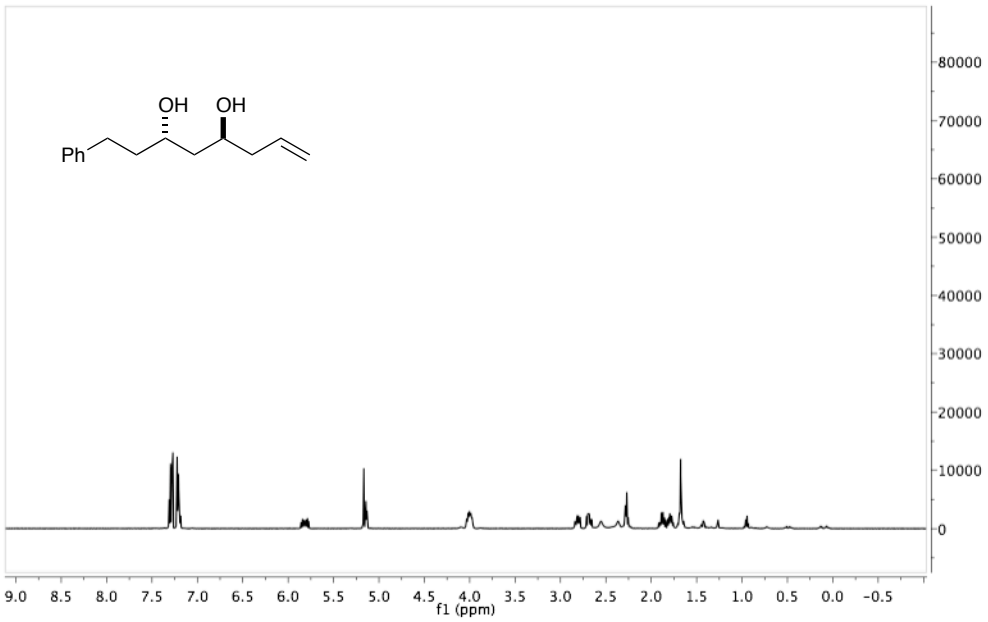
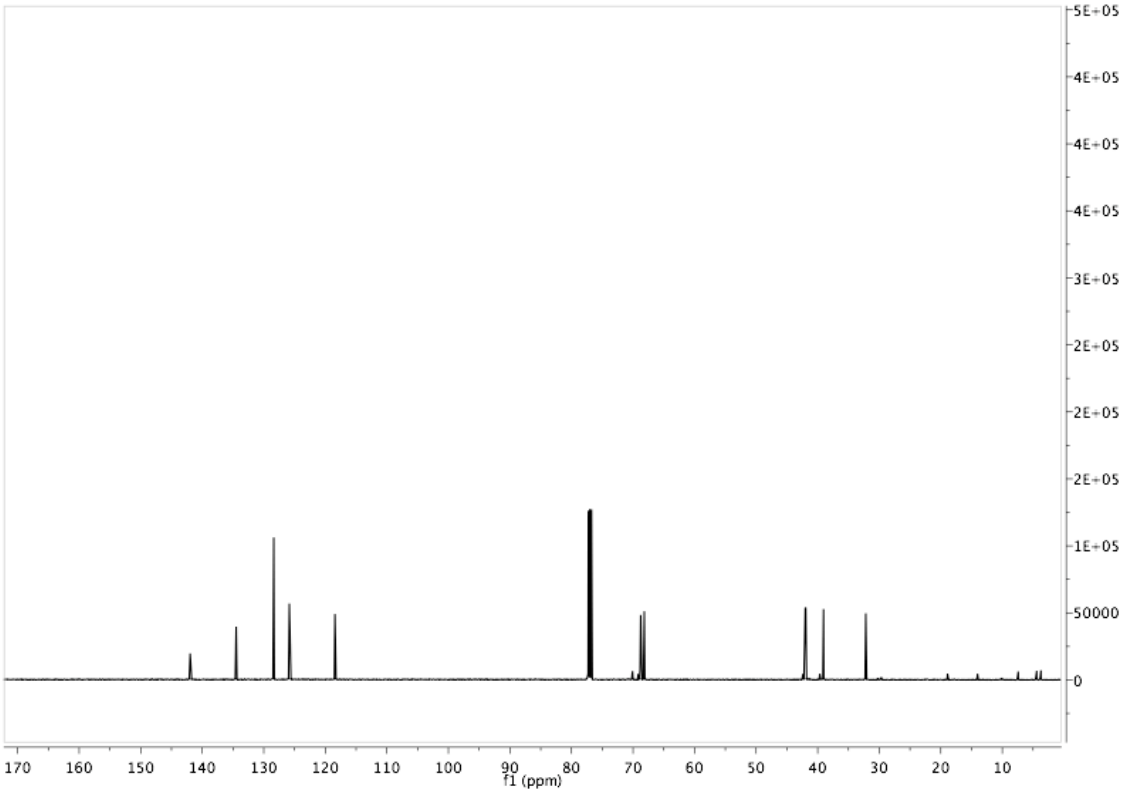
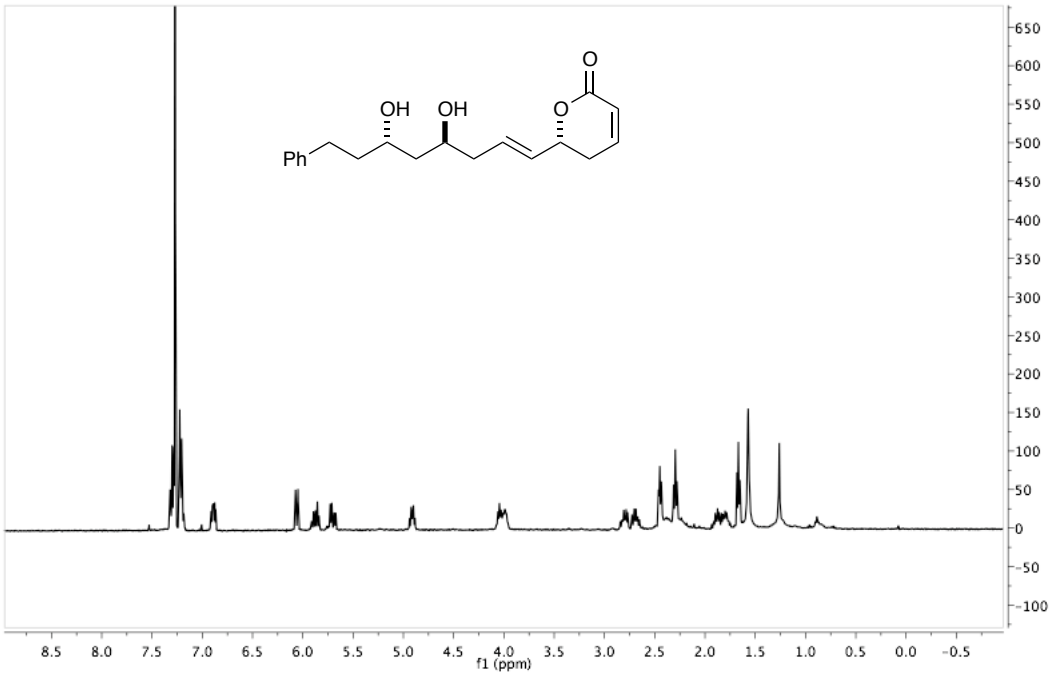
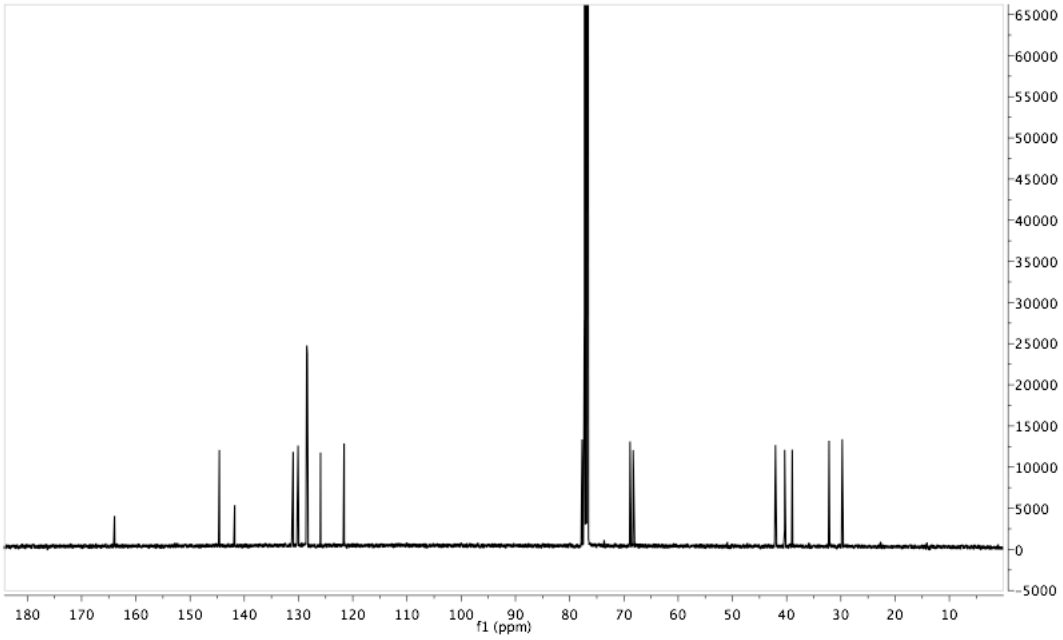
(3*S*,5*S*)-1-phenyloct-7-ene-3,5-diol (3.92)



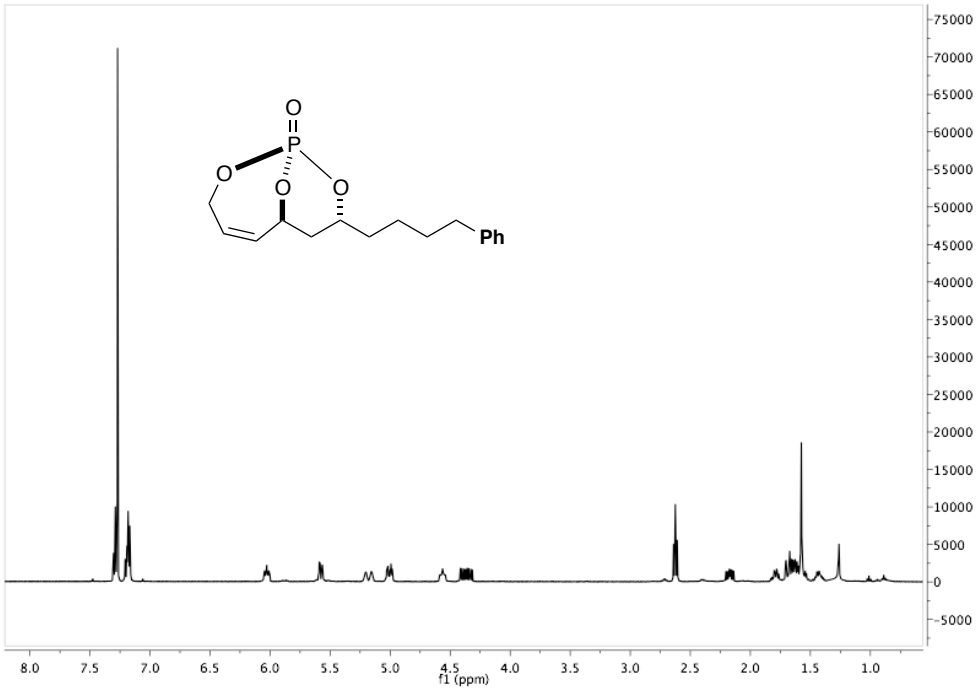


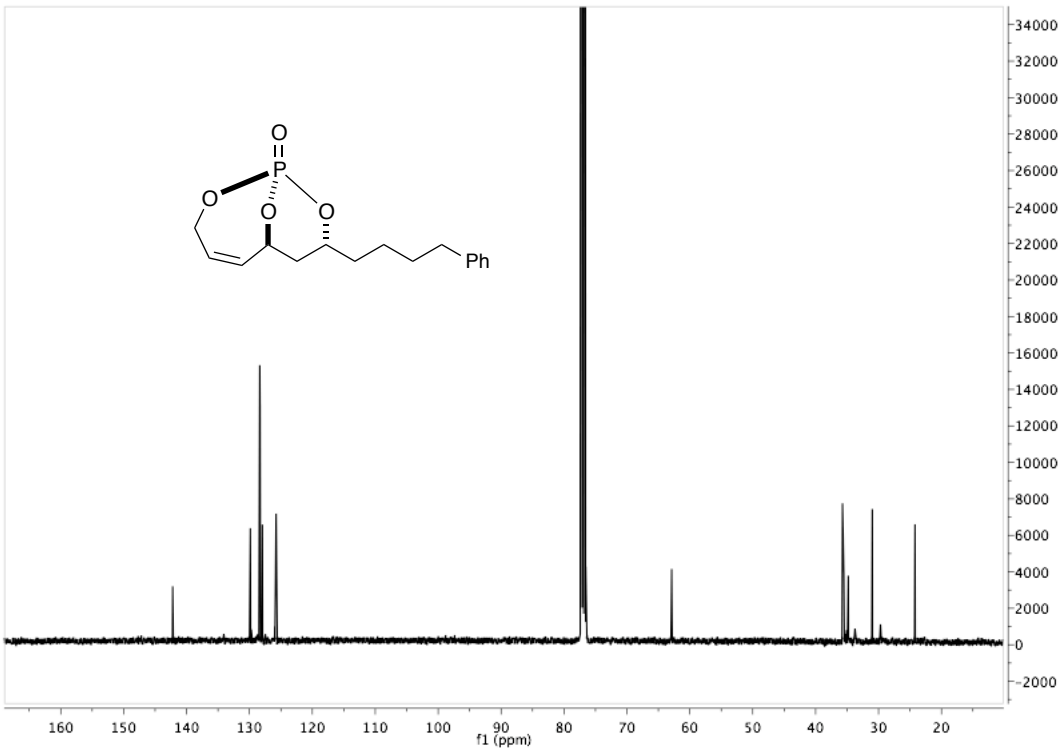
(*R*)-6-((4*S*,6*S*,*E*)-4,6-dihydroxy-8-phenyloct-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one– (+)-Strictifolione (3.1).





(1*S*,6*S*,8*R*)-8-(4-phenylbutyl)-2,9,10-trioxa-1phosphabicyclo[4.3.1]dec-4-ene 1-oxide (3.98).

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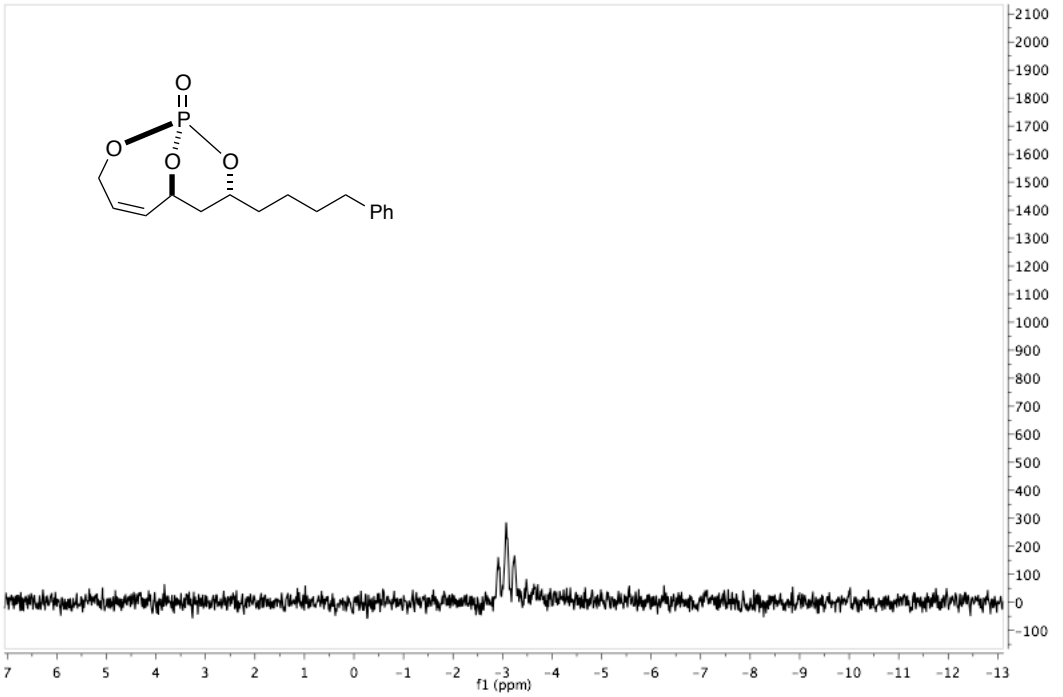
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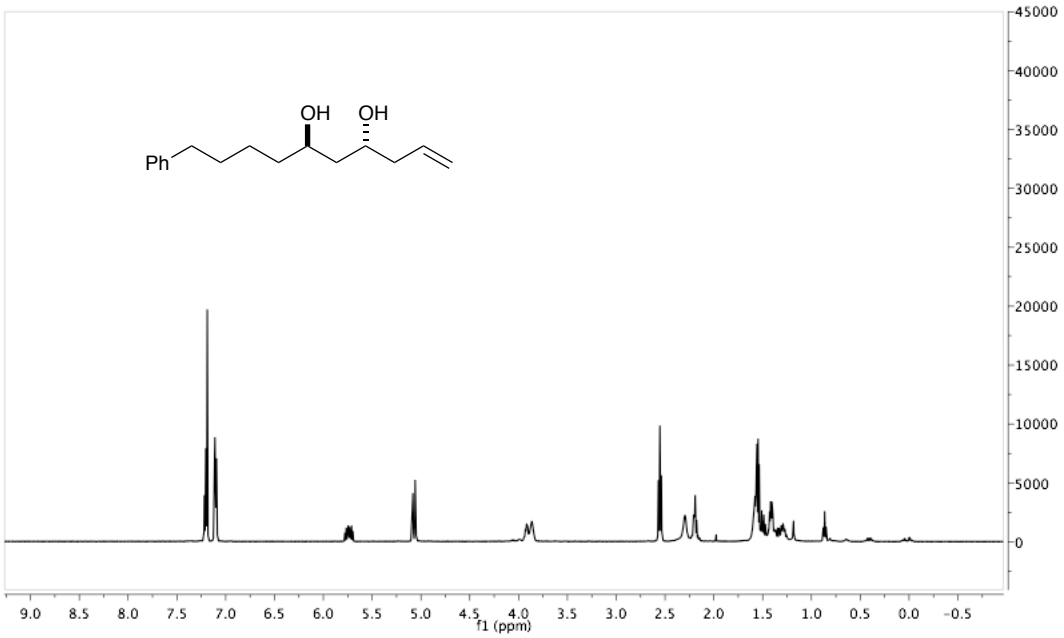
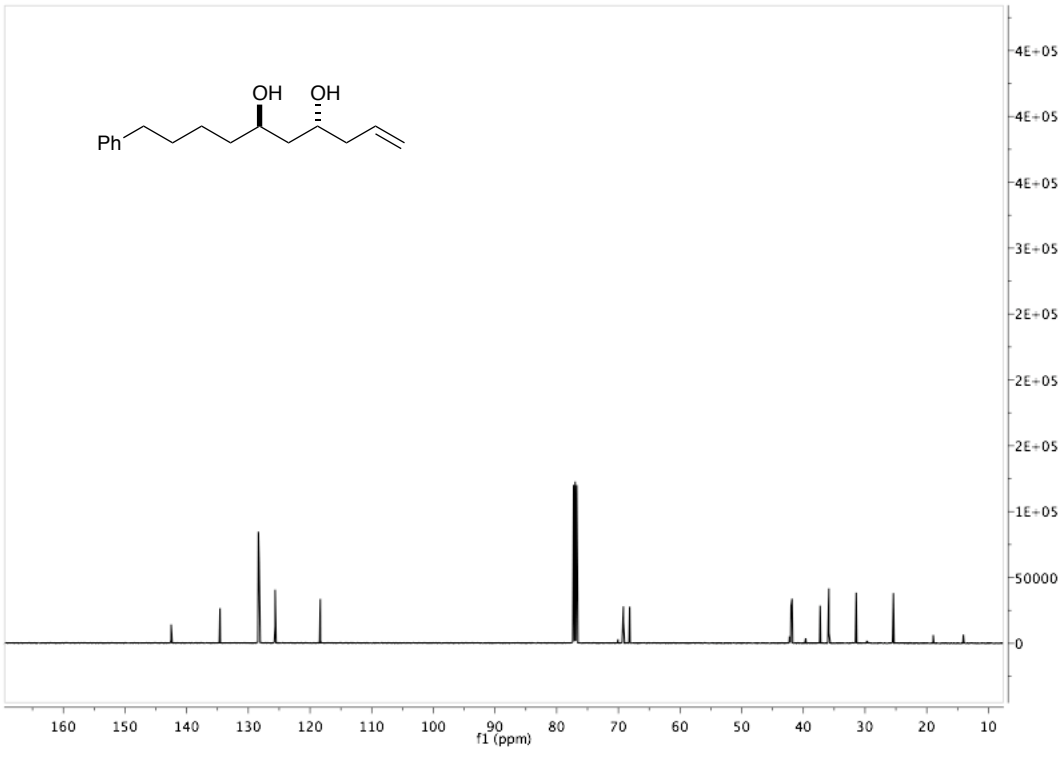
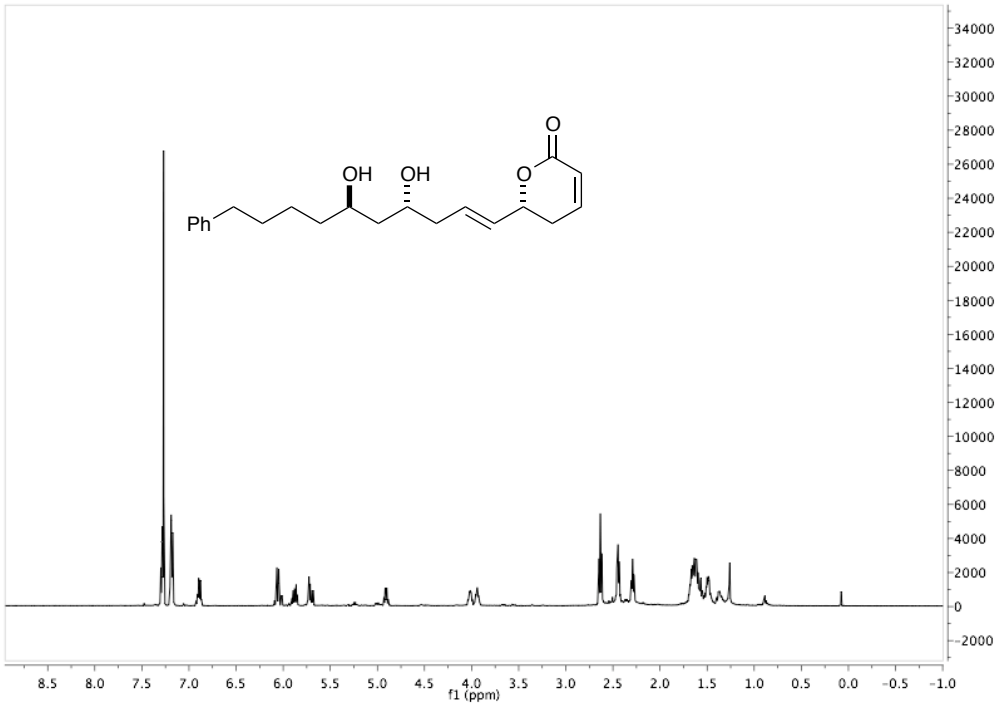
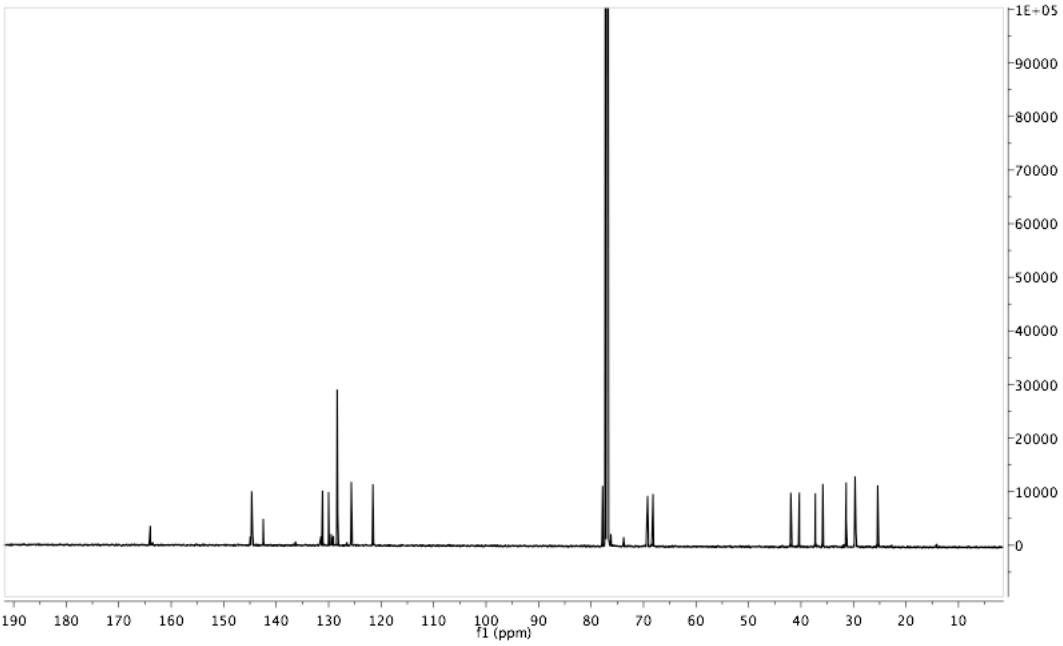
(4*R*,6*R*)-10-phenyldec-1-ene-4,6-diol (3.97)





(*R*)-6-((4*R*,6*R*,*E*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (3.2).





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Appendix

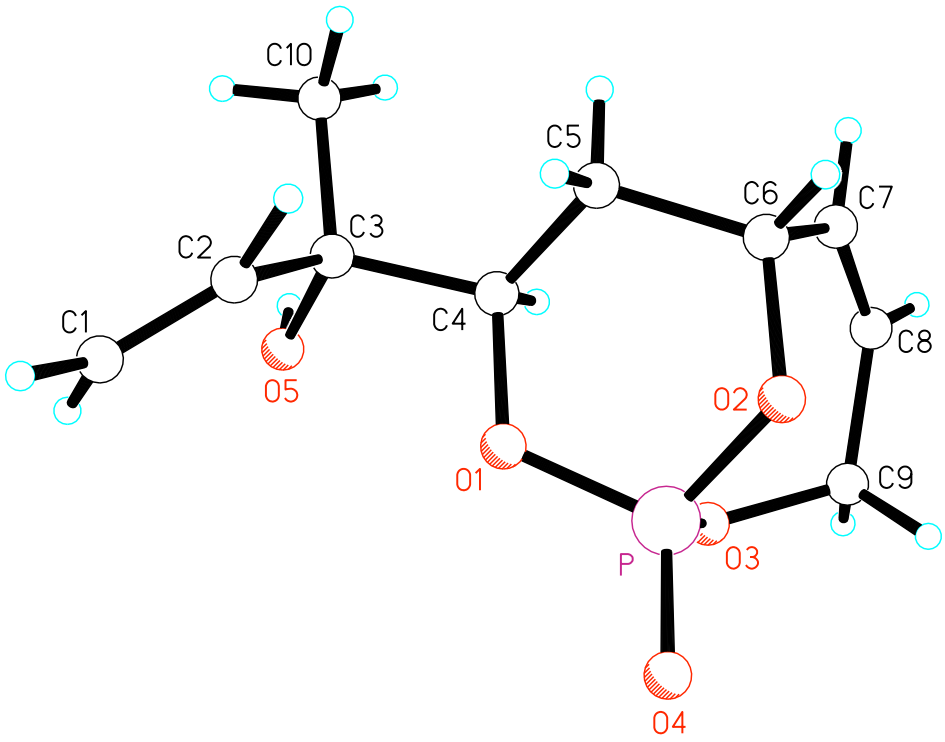
C10
C5
C6
C7
C3
C2
C1
C4
C8
O5
O2
O1
C9
P
O3
O4

Table 1. Crystal data and structure refinement for C10H15O5P.

Identification code	q16c	
Empirical formula	C10 H15 O5 P	
Formula weight	246.19	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5476(3) Å	⟨= 90°.
	b = 11.7948(4) Å	®= 90°.
	c = 12.7172(5) Å	© = 90°.
Volume	1132.12(7) $Å^3$	
Z	4	
Density (calculated)	1.444 Mg/m^3	
Absorption coefficient	2.229 mm^{-1}	
F(000)	520	
Crystal size	0.32 x 0.08 x 0.06 mm^3	
Theta range for data collection	5.11 to 69.31°.	
Index ranges	-7<=h<=8, -13<=k<=12, -15<=l<=14	
Reflections collected	9802	
Independent reflections	1997 [R(int) = 0.0246]	
Completeness to theta = 66.00°	98.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.752	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1997 / 0 / 206	
Goodness-of-fit on F^2	1.092	
Final R indices [I>2sigma(I)]	R1 = 0.0224, wR2 = 0.0601	
R indices (all data)	R1 = 0.0225, wR2 = 0.0602	
Absolute structure parameter	0.081(17)	
Extinction coefficient	0.0009(4)	
Largest diff. peak and hole	0.239 and -0.178 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C10H15O5P. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P	2780(1)	4469(1)	2025(1)	17(1)
O(1)	4339(1)	4360(1)	2831(1)	19(1)
O(2)	2268(1)	3237(1)	1666(1)	19(1)
O(3)	3686(2)	5046(1)	1050(1)	21(1)
O(4)	1271(1)	5080(1)	2463(1)	22(1)
O(5)	7931(2)	4854(1)	3352(1)	24(1)
C(1)	6633(3)	4258(2)	5290(1)	35(1)
C(2)	6402(2)	3567(1)	4482(1)	28(1)
C(3)	7220(2)	3733(1)	3412(1)	23(1)
C(4)	5824(2)	3618(1)	2532(1)	19(1)
C(5)	5092(2)	2441(1)	2302(1)	22(1)
C(6)	3707(2)	2439(1)	1418(1)	21(1)
C(7)	4429(2)	2660(1)	335(1)	21(1)
C(8)	4230(2)	3562(1)	-275(1)	22(1)
C(9)	3340(2)	4667(1)	-22(1)	22(1)
C(10)	8683(2)	2851(1)	3244(1)	25(1)

Table 3. Bond lengths [Å] and angles [°] for C10H15O5P.

P-O(4)	1.4589(11)
P-O(1)	1.5656(11)
P-O(3)	1.5707(11)
P-O(2)	1.5718(10)
O(1)-C(4)	1.4720(17)
O(2)-C(6)	1.4715(17)
O(3)-C(9)	1.4587(17)
O(5)-C(3)	1.4292(18)
O(5)-H(5O)	0.89(3)
C(1)-C(2)	1.323(3)
C(1)-H(1A)	0.98(2)
C(1)-H(1B)	1.01(2)
C(2)-C(3)	1.507(2)
C(2)-H(2)	1.109(16)
C(3)-C(10)	1.532(2)
C(3)-C(4)	1.542(2)
C(4)-C(5)	1.522(2)
C(4)-H(4)	0.953(18)
C(5)-C(6)	1.536(2)
C(5)-H(5A)	0.96(2)
C(5)-H(5B)	1.02(2)
C(6)-C(7)	1.504(2)
C(6)-H(6)	0.938(19)
C(7)-C(8)	1.325(2)
C(7)-H(7)	0.93(2)
C(8)-C(9)	1.501(2)
C(8)-H(8)	0.94(2)
C(9)-H(9A)	1.01(2)
C(9)-H(9B)	0.989(19)
C(10)-H(10A)	0.98(2)
C(10)-H(10B)	0.95(2)
C(10)-H(10C)	0.97(2)

O(4)-P-O(1)	112.14(6)
O(4)-P-O(3)	115.32(6)
O(1)-P-O(3)	103.03(6)
O(4)-P-O(2)	112.06(6)
O(1)-P-O(2)	107.36(6)
O(3)-P-O(2)	106.21(5)
C(4)-O(1)-P	116.88(9)
C(6)-O(2)-P	118.19(9)
C(9)-O(3)-P	121.75(9)
C(3)-O(5)-H(5O)	110.3(14)
C(2)-C(1)-H(1A)	123.2(12)
C(2)-C(1)-H(1B)	123.2(13)
H(1A)-C(1)-H(1B)	113.6(18)
C(1)-C(2)-C(3)	124.56(16)
C(1)-C(2)-H(2)	131.3(8)
C(3)-C(2)-H(2)	103.4(8)
O(5)-C(3)-C(2)	108.77(12)
O(5)-C(3)-C(10)	110.47(13)
C(2)-C(3)-C(10)	109.48(13)
O(5)-C(3)-C(4)	107.45(12)
C(2)-C(3)-C(4)	111.31(13)
C(10)-C(3)-C(4)	109.34(12)
O(1)-C(4)-C(5)	108.38(12)
O(1)-C(4)-C(3)	106.30(11)
C(5)-C(4)-C(3)	117.89(13)
O(1)-C(4)-H(4)	106.8(11)
C(5)-C(4)-H(4)	109.0(10)
C(3)-C(4)-H(4)	108.0(11)
C(4)-C(5)-C(6)	112.93(12)
C(4)-C(5)-H(5A)	110.3(11)
C(6)-C(5)-H(5A)	104.2(12)
C(4)-C(5)-H(5B)	108.8(11)
C(6)-C(5)-H(5B)	108.9(11)
H(5A)-C(5)-H(5B)	111.7(15)

O(2)-C(6)-C(7)	110.69(12)
O(2)-C(6)-C(5)	110.08(11)
C(7)-C(6)-C(5)	115.10(13)
O(2)-C(6)-H(6)	103.5(11)
C(7)-C(6)-H(6)	109.1(11)
C(5)-C(6)-H(6)	107.7(11)
C(8)-C(7)-C(6)	129.37(14)
C(8)-C(7)-H(7)	120.7(13)
C(6)-C(7)-H(7)	110.0(13)
C(7)-C(8)-C(9)	128.49(14)
C(7)-C(8)-H(8)	120.1(13)
C(9)-C(8)-H(8)	111.4(13)
O(3)-C(9)-C(8)	112.73(13)
O(3)-C(9)-H(9A)	109.9(11)
C(8)-C(9)-H(9A)	110.7(11)
O(3)-C(9)-H(9B)	102.3(11)
C(8)-C(9)-H(9B)	113.7(11)
H(9A)-C(9)-H(9B)	107.1(15)
C(3)-C(10)-H(10A)	114.1(13)
C(3)-C(10)-H(10B)	109.1(13)
H(10A)-C(10)-H(10B)	107.3(18)
C(3)-C(10)-H(10C)	106.0(12)
H(10A)-C(10)-H(10C)	109.9(18)
H(10B)-C(10)-H(10C)	110.5(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for C10H15O5P. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P	17(1)	17(1)	17(1)	0(1)	2(1)	0(1)
O(1)	19(1)	20(1)	19(1)	-4(1)	0(1)	3(1)
O(2)	18(1)	18(1)	22(1)	-1(1)	2(1)	-2(1)
O(3)	25(1)	19(1)	19(1)	-1(1)	3(1)	-4(1)
O(4)	21(1)	23(1)	23(1)	-1(1)	2(1)	3(1)
O(5)	21(1)	19(1)	31(1)	-4(1)	3(1)	-2(1)
C(1)	33(1)	45(1)	28(1)	-6(1)	2(1)	-4(1)
C(2)	26(1)	32(1)	25(1)	2(1)	-2(1)	-3(1)
C(3)	23(1)	21(1)	24(1)	-3(1)	-2(1)	-1(1)
C(4)	19(1)	20(1)	20(1)	-2(1)	3(1)	3(1)
C(5)	24(1)	19(1)	22(1)	1(1)	1(1)	2(1)
C(6)	22(1)	14(1)	26(1)	-2(1)	1(1)	-1(1)
C(7)	20(1)	21(1)	22(1)	-7(1)	2(1)	0(1)
C(8)	21(1)	26(1)	19(1)	-4(1)	3(1)	-2(1)
C(9)	26(1)	24(1)	17(1)	0(1)	1(1)	0(1)
C(10)	22(1)	20(1)	34(1)	-2(1)	-4(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C10H15O5P.

	x	y	z	U(eq)
H(5O)	8940(30)	4854(19)	2980(18)	38(6)
H(1A)	7290(30)	4972(19)	5241(16)	36(5)
H(1B)	6100(30)	4117(19)	6009(17)	41(6)
H(2)	5820(20)	2705(14)	4434(12)	10(4)
H(4)	6320(20)	3923(14)	1904(14)	15(4)
H(5A)	6010(30)	1954(16)	2047(15)	23(4)
H(5B)	4520(30)	2127(17)	2972(16)	23(4)
H(6)	3140(20)	1730(15)	1424(14)	18(4)
H(7)	5100(30)	2049(17)	114(16)	30(5)
H(8)	4650(30)	3550(18)	-967(17)	28(5)
H(9A)	2020(30)	4613(16)	-144(14)	26(5)
H(9B)	3780(30)	5312(16)	-445(14)	20(4)
H(10A)	8310(30)	2070(20)	3375(17)	37(5)
H(10B)	9080(30)	2890(18)	2536(18)	32(5)
H(10C)	9630(30)	3055(17)	3721(16)	25(5)

Table 6. Torsion angles [°] for C10H15O5P.

O(4)-P-O(1)-C(4)	171.25(10)
O(3)-P-O(1)-C(4)	-64.12(11)
O(2)-P-O(1)-C(4)	47.75(11)
O(4)-P-O(2)-C(6)	-167.35(9)
O(1)-P-O(2)-C(6)	-43.80(10)
O(3)-P-O(2)-C(6)	65.89(11)
O(4)-P-O(3)-C(9)	-100.78(12)
O(1)-P-O(3)-C(9)	136.71(11)
O(2)-P-O(3)-C(9)	23.99(13)
C(1)-C(2)-C(3)-O(5)	-12.6(2)
C(1)-C(2)-C(3)-C(10)	108.2(2)
C(1)-C(2)-C(3)-C(4)	-130.81(18)
P-O(1)-C(4)-C(5)	-56.60(14)
P-O(1)-C(4)-C(3)	175.76(9)
O(5)-C(3)-C(4)-O(1)	-68.57(15)
C(2)-C(3)-C(4)-O(1)	50.42(16)
C(10)-C(3)-C(4)-O(1)	171.50(12)
O(5)-C(3)-C(4)-C(5)	169.66(13)
C(2)-C(3)-C(4)-C(5)	-71.34(17)
C(10)-C(3)-C(4)-C(5)	49.74(18)
O(1)-C(4)-C(5)-C(6)	58.94(16)
C(3)-C(4)-C(5)-C(6)	179.64(12)
P-O(2)-C(6)-C(7)	-79.44(13)
P-O(2)-C(6)-C(5)	48.94(14)
C(4)-C(5)-C(6)-O(2)	-55.47(16)
C(4)-C(5)-C(6)-C(7)	70.45(17)
O(2)-C(6)-C(7)-C(8)	16.0(2)
C(5)-C(6)-C(7)-C(8)	-109.64(19)
C(6)-C(7)-C(8)-C(9)	5.4(3)
P-O(3)-C(9)-C(8)	-74.05(15)
C(7)-C(8)-C(9)-O(3)	39.0(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for C10H15O5P [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5O)...O(4)#1	0.89(3)	1.90(2)	2.7754(15)	166(2)

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z